May 22, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Atherectomy ablative angioplasty catheter
Brand Name	Peripheral Rotablator PRO
Applicant	Boston Scientific Japan K.K.
Date of Application	November 30, 2022 (Application for marketing approval)

Results of Deliberation

In its meeting held on May 22, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with the designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 4 years. The following approval conditions should be attached.

Approval Conditions

1. The product should only be used for eligible patients selected by physicians and medical teams with adequate knowledge and experience in endovascular treatment for chronic limb-threatening ischemia as well as necessary operational skills with the product and knowledge about procedure-related complications, at medical institutions with an established treatment system. To this end, the applicant is required to take appropriate measures including the provision of training programs and the dissemination of the proper use guidelines jointly prepared with relevant academic societies.

2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are accrued from a specified number of patients, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.

Review Report

May 12, 2025

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Atherectomy ablative angioplasty catheter
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Reviewing Office	Office of Medical Devices II

Review Results

May 12, 2025

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Atherectomy ablative angioplasty catheter
Brand Name	Peripheral Rotablator PRO
Applicant	Boston Scientific Japan K.K.
Date of Application	November 30, 2022

Results of Review

The Peripheral Rotablator PRO (or the product) is an atherectomy catheter for rotational angioplasty (hereinafter referred to as "atherectomy device") to ablate atherosclerotic plaques and heavily calcified below-the-knee stenotic lesions in patients with chronic limb-threatening ischemia (CLTI) via a percutaneous approach. The product primarily consists of an advancer/catheter for the ablation of lesions and a console that controls catheter movement. The advancer/catheter and console, modified from the approved "Rotablator PRO" for coronary artery lesions (Approval No. 23000BZX00060000), provide different burr size selection and recommended/standard rotational speeds. The product comes with guidewires and wire clips that are identical to those of the "Rotablator" (Approval No. 20900BZY00356000).

The applicant submitted non-clinical data supporting stability, durability, and performance of the product. The data revealed no particular problems.

The clinical data submitted included the results from a multicenter, investigator-initiated study (the RESCUE-BTK study) conducted at 10 study centers in Japan to evaluate the safety and efficacy of the "Rotablator," the preceding atherectomy device for adjunctive use in balloon angioplasty in patients with critical limb ischemia (CLI, or CLTI in the current guidelines) in whom angioplasty failed. The study targeted CLI patients with unsuccessful pre-trial balloon angioplasty who had a target lesion ≥2 mm to ≤4 mm in reference vessel diameter and <100 mm in length (per lesion) located between the distal popliteal arteries and the distal below-the-knee arteries. The primary endpoint was "post-procedural success rate of balloon angioplasty" based on the fulfillment of 3 requirements in the core laboratory assessment including (1) residual stenosis of <50% (visual and quantitative angiographic analysis); (2) absence of a delay in flow

in angiography or vessel perforation in the target artery; and (3) brisk antegrade flow to the foot (peripheral). The result of the primary endpoint, 94.1% (16 of 17 patients; 95% confidence interval [CI], 71.3%-99.9%), met the prespecified target of 50%. No patients underwent major amputation of the affected limb within 24 weeks post-trial procedure. The improvements in visual analogue scale (VAS), skin perfusion pressure (SPP) of the affected limb, Rutherford category, and EuroQol 5-Dimension 5-Level (EQ-5D-5L) were maintained. The proportion of patients with healed wounds was 50% (6 of 12 patients) and the proportion of healed wounds was 66.7% (12 of 18 wounds), which are acceptable as balloon angioplasty in below-the-knee arteries in patients with CLTI. The results are demonstrative of the efficacy of the product in patients with CLTI in whom conventional balloon angioplasty for below-the-knee calcified lesions is unlikely to succeed.

In the study, delay in flow for which a causal relationship to device malfunctions (guidewire fracture, retained fragments) could not be ruled out occurred in 2 of 17 patients (11.8%), delay in flow likely attributable to distal embolization occurred in 2 of 17 patients (11.8%), distal embolization in 1 of 17 patients (5.9%), and vascular dissection occurred in 3 of 17 patients (17.6%). The incidences of some events tended to be high compared to those observed in patients with CLTI after balloon angioplasty without atherectomy devices or those who were treated with the “Rotablator” for the coronary arteries. However, this tendency is considered attributable to the target lesions in this study, with severer calcification that would preclude the success of below-the-knee balloon angioplasty. Therefore, the higher incidences were acceptable because the risk can be reduced by appropriate post-marketing safety measures.

By Week 24 post-procedure, re-intervention occurred in 6 of 17 patients (35.3%), death in 2 of 17 patients (11.8%), and serious or non-serious adverse events associated with the procedure/device in 4 of 17 patients (23.5%). There were no particular problems with these results compared with the current below-the-knee balloon angioplasty in patients with CLTI.

Currently in Japan, there is no effective treatment options for patients with a severely calcified lesion that hampers balloon crossing or dilatation, despite their eligibility for revascularization. Patients are forced to choose major amputation or suffer from poor prognosis. The use of the product is clinically meaningful in patients with CLTI who are in urgent need of below-the-knee endovascular treatment for revascularization. Therefore, it is useful to make the product available in Japan.

The Peripheral Rotablator PRO is the first atherectomy device to be introduced in Japan for patients with CLTI having calcified lesions in the below-knee arteries. As it mechanically ablates

calcified lesions, the risks of distal embolization and vessel damage by plaque fragments are inevitable. For effective and safe introduction of the product, it is important that it be used for patients at high risk for surgical bypass procedure for whom balloon angioplasty would be beneficial but unlikely to succeed. Eligible patients need to be carefully selected by physicians and medical teams with expertise in CLTI treatment and adequate knowledge and experience in below-the-knee endovascular treatment and lower extremity atherectomy. Treating physicians should gain necessary knowledge and skills pertaining to the product and the procedure through training. Complications such as distal embolization may require immediate intervention including surgery. Foot care including wound management is essential in the treatment of CLTI. Therefore, the treatment with the Peripheral Rotablator PRO should be performed only at medical institutions with an established system capable of responding to such cases.

Also important are appropriate patient selection in post-marketing practice according to proper product use, continual assessment through a post-marketing use-results survey to ensure product safety and efficacy in the treatment of below-the-knee calcified lesions in patients with CLTI in whom balloon angioplasty is unlikely to succeed, and additional risk mitigation measures promptly taken when necessary.

Based on the results of review, PMDA has concluded that the product may be approved for the following intended use with the approval conditions attached below, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The Peripheral Rotablator PRO is intended for adjunctive use in endovascular treatment for patients with chronic limb-threatening ischemia. The product percutaneously approaches calcified lesions in the below-the-knee arteries that impede the crossing or inflation of balloon catheter for percutaneous transluminal angioplasty, thereby ablating atherosclerotic plaques or stenotic lesions.

Approval Conditions

1. The product should only be used for eligible patients selected by physicians and medical teams with adequate knowledge and experience in endovascular treatment for chronic limb-threatening ischemia as well as necessary operational skills with the product and knowledge about procedure-related complications, at medical institutions with an established treatment system. To this end, the applicant is required to take appropriate measures including the

provision of training programs and the dissemination of the proper use guidelines jointly prepared with the relevant academic societies.

2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are accrued from a specified number of patients, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.

Review Report

May 12, 2025

Product for Review

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Atherectomy ablative angioplasty catheter
Brand Name	Peripheral Rotablator PRO
Applicant	Boston Scientific Japan K.K.
Date of Application	November 30, 2022
Proposed Intended Use	The Peripheral Rotablator PRO is intended for adjunctive use in endovascular treatment for patients with atherosclerotic lower extremity artery disease. The product percutaneously approaches the below-the-knee arteries, thereby ablating atherosclerotic plaques or stenotic lesions.

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List of Abbreviations

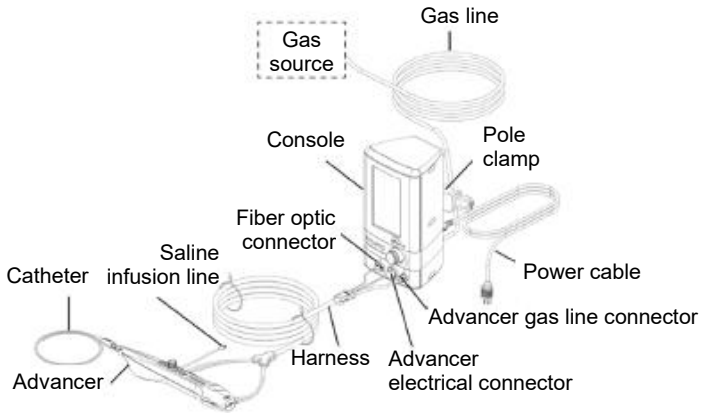
ABI	Ankle Brachial Index
CLI	Critical Limb Ischemia
CLTI	Chronic Limb-Threatening Ischemia
DSA	Digital Subtraction Angiography
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQol 5-Dimension 5-Level
GCP	Good Clinical Practice
IVR	Interventional Radiology
LEAD	Lower Extremity Artery Disease
PTA	Percutaneous Transluminal Angioplasty
QOL	Quality of Life
SPP	Skin Perfusion Pressure
VAS	Visual Analogue Scale
WIfI	Wound, Ischemia, and foot Infection

I. Product Overview

The Peripheral Rotablator PRO (or the product) is an atherectomy catheter for rotational angioplasty (hereinafter referred to as "atherectomy device") to ablate atherosclerotic plaques and heavily calcified below-the-knee stenotic lesions in patients with chronic limb-threatening ischemia (CLTI) via a percutaneous approach. The product primarily consists of an advancer/catheter for the ablation of lesions and a console that controls catheter movement (Figure 1). The advancer/catheter and console, modified from the approved "Rotablator PRO" (Approval No. 23000BZX00060000) for coronary artery lesions, provide different burr size selection and recommended/standard rotational speeds. The diamond-coated burr of the catheter moves coaxially over a guidewire and the burr rotates at high speeds, ablating plaques and calcifications. Burrs are available in 6 sizes (1.25, 1.50, 1.75, 2.00, 2.25, 2.50 mm in diameter). The guidewires and wire clips to be used with the atherectomy device are identical to those of the "Rotablator" (Approval No. 20900BZY00356000). The ablation particles produced are 2 to 5 μm in size,[1] which is smaller than a red blood cell or white blood cell in peripheral blood, and presumably comparable to the size of a platelet.[2]

Advancer/catheter
(top, overall device; bottom, enlarged view of the burr)

Console



System overview

Figure 1. Appearance of Peripheral Rotablator PRO

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the present application and the applicant's responses to inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the Peripheral Rotablator PRO declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Atherosclerotic lower extremity artery disease is an atherosclerotic peripheral arterial disease, accounting for the majority of lower extremity artery disease (LEAD). The treatment strategy for LEAD varies greatly depending on the symptoms and the severity of ischemia. Chronic limb threatening ischemia (CLTI) is defined as 2 or more weeks of rest pain, lower extremity ulcers, or necrosis due to ischemia without improvement, and is a collective term to refer to the condition of lower extremities requiring therapeutic intervention, presenting with lower limb ischemia, tissue deficits, nerve disorders, infections, etc., carrying an increased risk of amputation. Previously, CLTI was called as critical limb ischemia (CLI). However, with increasing number of patients with diabetes mellitus, not only ischemia but also the location or size of wounds and infection can significantly affect lower limb outcomes. For this reason, CLTI has been accepted as the term that reflects the risk of lower extremity amputation more accurately.[3] The goals of CLTI treatment are preventing amputation, preserving limb function, eliminating pain, and healing wounds. For patients with suspected CLTI who do not require emergency major amputation, revascularization (surgical or endovascular treatment) is the first-line strategy. However, since most patients with CLTI are the elderly and often have multiple comorbidities and significant frailty, major amputation or palliative care, rather than revascularization, may be considered for patients whose limbs are unlikely to recover. If a patient with CLTI is found to be eligible for revascularization, surgical or endovascular treatment is selected after risk assessment for revascularization (patient risk, severity in the affected limb, anatomical severity).[4] Typically, the presence of blood flow disturbance in 2 or more areas of iliac, femoral, and below-the-knee arteries results in CLTI. However, as there are many patients with diabetes mellitus and patients on dialysis in Japan, it is not uncommon for isolated below-the-knee lesions to lead to CLTI. It has been reported that approximately half of the patients with CLTI had isolated below-the-knee lesions.[5] In the SPINACH study, which enrolled 548 patients with CLTI in Japan from 2012 to

2013, below-the-knee surgical revascularization and endovascular treatment accounted for 78% and 72%, respectively.[6] According to the data from the Japan Critical Limb Ischemia Database (JCLIMB), of the revascularization cases performed in 3,505 patients with CLTI at vascular surgery institutions over 5 years between 2013 and 2017, surgical revascularization alone accounted for 45.9%, endovascular treatment alone accounted for 46.8%, and hybrid (surgical and endovascular) accounted for 7.2%. Among these, with respect to surgical revascularization, 43% of the procedures were performed in below-the-knee arteries while with respect to endovascular treatment, 39% of the procedures were performed in below-the-knee arteries.[7]

Endovascular treatment by classic balloon angioplasty has been widely performed to treat below-the-knee lesions in patients with CLTI; however, long-term patency is extremely low. The clinical practice guidelines in Japan recommend to consider below-the-knee artery endovascular treatment (recommended class IIa, evidence level C) for patients with CLTI with life prognosis of <2 years or who do not have autogenous veins usable.[3] In addition, there are patients whose below-the-knee lesions cannot be successfully treated by balloon angioplasty alone, which is a common problem associated with revascularization. It has been reported that revascularization was unsuccessful in 5.8% of patients not on dialysis and 12.3% of those on dialysis.[8] In many of unsuccessful cases, highly calcified lesions hampers balloon crossing or dilatation. Most of these cases are ineligible for surgical bypass, and there are no other effective treatments in Japan. Consequently, patients have no alternative but to have major amputation or to be placed under observation where major amputation is no longer an option. Based on the meta-analysis results from 6,118 patients with CLTI receiving conservative treatment, the outcomes of cases with unsuccessful treatment were amputation in 1 year in ≥95% of patients, compared to 25% if treated by revascularization (surgical or endovascular treatment).[9]

The Peripheral Rotablator PRO reaches below-the-knee lesions percutaneously to ablate atherosclerotic plaques or calcified stenosis with its high-speed rotating burr tip. The “Rotablator” (Approval No. 20900BZY00356000; approval date, May 14, 1997) and the “Rotablator PRO,” the successor model (Approval No. 23000BZX00060000; approval date, March 15, 2018), were approved as atherectomy devices indicated for the treatment of calcified and other stenotic lesions in coronary arteries, and have been used clinically. The Peripheral Rotablator PRO was developed for use in peripheral vessels of the lower extremities, with its burr size selection and recommended/standard rotational speeds modified from those of the Rotablator PRO (Approval No. 23000BZX00060000) (Table 1).

Table 1. Comparison with similar medical devices

	Rotablator (study device in the clinical trial)		Rotablator PRO		Peripheral Rotablator PRO	
Indication	Coronary arteries		Coronary arteries		Below-the-knee arteries	
Catheter dimension[1]	Effective length: 135[redacted] cm Sheath max diameter: 1.52 mm Burr diameter: 1.25, 1.50, 1.75, 2.00, 2.15, 2.25, 2.38, 2.50 mm		Effective length: 135[redacted] cm Sheath diameter: 1.42[redacted] mm Burr diameter: 1.25, 1.50, 1.75, 2.00, 2.15, 2.25, 2.38, 2.50 mm		Effective length: 135[redacted] cm Sheath diameter: 1.42[redacted] mm Burr diameter: 1.25, 1.50, 1.75, 2.00, 2.25, 2.50 mm	
Maximum recommended rotational speed at the time of operation check	Burr size: 1.25-2.0 mm; 190,000 RPM Burr size: ≥2.25 mm; 180,000 RPM		Burr size: 1.25-2.0 mm; 190,000 RPM Burr size: ≥2.25 mm; 180,000 RPM		Burr size: 1.25-2.0 mm; 190,000 RPM Burr size: ≥2.25 mm; 180,000 RPM	
Recommended speed to be adjusted in clinical use[2]	Burr size (mm)	Speed (RPM)	Burr size (mm)	Speed (RPM)	Burr size (mm)	Speed (RPM)
	1.25-2.0	160,000-180,000	1.25-2.0	160,000-180,000	1.25-2.0	140,000-180,000
	≥2.25	140,000-160,000	≥2.25	140,000-160,000	≥2.25	140,000-160,000
Console features	• Foot pedal		• Rotational speed can be controlled with the advancer button • Digital display has been adopted • Has a clamp to secure the console to an IV infusion pole		• Rotational speed can be controlled with the advancer button • Digital display has been adopted • Has a clamp to secure the console to an IV infusion pole	

[1.] The Peripheral Rotablator PRO does not include 2.15 mm and 2.38 mm burrs. The selection of burr sizes differs from those for the coronary indication.

[2.] The recommended speed to be adjusted specified in the instruction for use for the Peripheral Rotablator PRO differs from that for the "Rotablator PRO" (for "Rotablator PRO," the lower limit varies between burrs: 160,000 RPM for burr size 1.25-2.0 mm, 140,000 RPM for burr size ≥2.25 mm). The same lower limit of 140,000 RPM is specified for all burr sizes for the Peripheral Rotablator PRO, taking into account clinical use.[10]

In Japan, there was a report that the additional use of the "Rotablator" led to the success of balloon dilatation" in all patients who had previously undergone unsuccessful balloon angioplasty for lower limb arteries including below-the-knee arteries.[11] The results suggested a high clinical need for Peripheral Rotablator PRO in patients with CLTI having lesions that hamper balloon crossing or dilatation. In this context, the investigator-initiated study (the RESCUE-BTK study; Japan Registry of Clinical Trials No. jRCT1090220313) was conducted in Japan targeting patients with CLI in whom the balloon angioplasty using the previous generation device, the "Rotablator," had resulted in failure for lesions located between the distal popliteal arteries and the distal below-the-knee arteries. The applicant has recently filed an application for approval for the Peripheral Rotablator PRO, the successor product, with data extrapolated from the clinical study results of the "Rotablator," which comprises the catheter identical to that of the Peripheral Rotablator PRO.

1.A.(2) Use in foreign countries

Table 2 shows the authorization/licensing status and sales of the product in other countries.

Table 2. Authorization/licensing status and sales (as of March 2025)

Country/ region	Type	Intended use	Date approved	Quantity sold
US	Advancer/ catheter[1]	Intended for percutaneous use in the peripheral vessels in patients with occlusive arteriosclerotic disease eligible for endovascular procedures	September 6, 2022	[redacted] pieces
	Console[2]	Console designed for use with ROTAPRO Rotational Atherectomy System	Indication for peripheral vessels: September 6, 2022 Indication for coronary arteries: March 19, 2018	[redacted] sets (including the use for coronary arteries)
	Guidewires[3]	Guidewires designed for use with Rotablator Rotational Atherectomy System	September 13, 2012	[redacted] pieces

[1.] The Peripheral Rotablator PRO (sales quantity from September 2022 to March 2025); [2.] "Rotablator PRO" (sales quantity from October 2020 to March 2025); [3.] "Rotablator" (sales quantity from October 2020 to March 2025)

1.A.(3) Malfunctions and adverse events outside Japan

Table 3, Table 4, and Table 5 show the incidences of malfunctions and adverse events associated with the product's advancer/catheter, console, and guidewires reported outside Japan. The console (Table 4) includes the results both in peripheral vessels and coronary arteries.

Table 3. Incidences of malfunctions and adverse events associated with the product (advancer/catheter) in other countries

Description	Number of cases	Incidence[1] (%)
Entrapment of burr on guidewire	[redacted]	0.041
Unable to reach desired rotational speed due to system failure (during set-up and operation test)		0.027
Stall (system)		0.027
Guidewire fracture		0.014
Burr becomes lodged in lesion		0.014
Shaft damage		0.014
Brake failure		0.014
Liquid leakage from device		0.014
Foreign object contamination		0.014
Vascular dissection		0.014

[1.] Incidence from September 2022 to March 2025. Incidence = (number of cases / total shipping quantity during the survey period [redacted]) × 100. The total shipping quantity includes the quantity for outside the US.

Table 4. Incidences of malfunctions and adverse events associated with the product (console) in other countries

Description	Number of cases	Incidence[1] (%)
Console speed instability	[redacted]	1.513
Unable to adjust speed		0.362
Unexpected screen display		0.296
Unexpected behavior in Dynaglide mode		0.296
Blank display/display failure		0.296
Rotational speed instability (system)		0.230
Audible sound from the device		0.197
Stall (system)		0.197
Unable to reach desired rotational speed due to system failure (during ablation)		0.132
Console damage/failure		0.132
Unable to reach desired rotational speed due to system failure (during set-up and operation test)		0.099
Abnormal noise of the system		0.099
Dynaglide mode malfunction		0.099
Electrical connector damage/failure		0.099
No rotational speed on the display		0.066
Gas/air leakage from the system		0.066
Unexpected movement		0.066
Display damage/failure		0.033
Gas line damage		0.033
The deceleration indicator on the screen remains ON		0.033
Loss of speed control knob		0.033
Does not respond to the advancer button		0.033
Power OFF failure		0.033
Thrombus		0.033
Decreased blood flow		0.033
Cardiac arrest		0.033
Death		0.033

[1] Incidence from October 2020 to March 2025. Incidence = (number of cases / total shipping quantity, [redacted]) × 100. The total shipping quantity includes the quantity for outside the US. Data on both indication, peripheral vessels and coronary arteries, are included. Because the console is not a single-use device, the incidence is only for reference purposes.

Table 5. Incidences of malfunctions and adverse events associated with the product (guidewire) in other countries

Description	Number of cases	Incidence[1] (%)
Entrapment of burr on guidewire	[redacted]	0.032
Kink		0.012
Guidewire fracture		0.012
Guidewire detachment		0.012
Entrapment		0.005
Contamination during use		0.002
Foreign material inclusion		0.002
Guidewire deformation		0.002
Guidewire does not move smoothly		0.002
Distal tip detachment		0.002
Vasospasm		0.002
Unretrievable device fragments		0.002
Additional intervention		0.002
Vessel perforation		0.002
Death		0.002

[1] Incidence from October 2020 to March 2025. Incidence = (number of cases / total shipping quantity during the survey period [redacted]) × 100. The total shipping quantity includes the quantity for outside the US.

1.B Outline of the review conducted by PMDA

Malfunctions and adverse events reported outside Japan associated with the catheter and guidewires will be evaluated in Section 6 together with the incidence. Given no events specific to peripheral vessels were expected, console-associated risks were considered comparable to that of the approved products. All reported cases of "console speed instability" were associated with coronary artery lesions, and no complications associated with the event were reported. Causes of the majority of malfunctions/events remained unidentified, but some were attributed to inappropriate use and failure of parts. The applicant explained their ongoing risk mitigation measures, i.e., communicating these incidents to product users through Information on Precautions, etc. or the package insert ("Information on Precautions, etc."), and instructing users to test and adjust the burr rotational speed before clinical use. The applicant's explanation is acceptable.

2. Design and Development

2.(1). Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications for the product pertaining to the advancer/catheter include rotational speed [redacted], continuous operation time [redacted], catheter tensile strength, and saline flow rate.

As mentioned earlier, the advancer/catheter and console of the product provide burr size selection and rotational speeds partially modified from the approved "Rotablator PRO" such as the standard value of [redacted] in the rotational speed [redacted] in performance specifications. The directions for use for both the Peripheral Rotablator PRO and the approved "Rotablator PRO" specify the same [redacted]. The product specifications have been set based on [redacted], and thus these changes do not affect device performance.

The proposed performance and safety specifications for the console consisted of deceleration display, pressure check, stall display [redacted] low-speed display [redacted].

The proposed performance and safety specifications for the overall system included biological safety, ethylene oxide gas sterilization residuals, endotoxins, electrical safety, and electromagnetic compatibility.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the performance and safety including modification from the "Rotablator PRO," and concluded that there were no particular problems.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

Data on the physicochemical properties were not submitted because they are included in the data on performance described later.

2.(2).B Outline of the review conducted by PMDA

PMDA concluded that it is appropriate to omit submission of data because physicochemical properties are evaluated in the section on performance.

2.(3) Electrical safety and electromagnetic compatibility

2.(3).A Summary of the data submitted

Based on comparability with the console and advancer of the "Rotablator PRO," data on the electrical safety and electromagnetic compatibility for the Peripheral Rotablator PRO were omitted.

2.(3).B Outline of the review conducted by PMDA

PMDA concluded that it is acceptable to omit submission of data based on comparability with the console and advancer of the "Rotablator PRO."

2.(4). Biological safety

2.(4).A Summary of the data submitted

Data on biological safety were omitted because the raw materials of the Peripheral Rotablator PRO directly or indirectly coming in contact with the body are the same as those for the advancer/catheter of the "Rotablator PRO."

2.(4).B Outline of the review conducted by PMDA

PMDA concluded that it is acceptable to omit submission of data given that the raw materials for the advancer/catheter are the same as those of the "Rotablator PRO."

2.(5) Stability and durability

2.(5).A Summary of the data submitted

The Peripheral Rotablator PRO is morphologically and structurally the same as the previous "Rotablator PRO" except for the modified burr size selection in the advancer/catheter," and the

raw materials remain unchanged. The manufacturing process and the sterilization method are also the same. Accordingly, the applicant submitted a self-declaration stating that the shelf life was specified after necessary stability evaluation was performed in accordance with the "Handling of Stability Studies Related to the Determination of the Shelf life in the Application for Marketing Approvals (Certifications) of Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012, issued by the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability of the product and concluded that there were no particular problems.

2.(6) Performance

2.(6).A Summary of the data submitted

The submitted data on the advancer/catheter and console included [redacted] that may affect the product performance when used in peripheral vessels, which were evaluated using an anatomy model of the lower limb vessels, taking into account the difference between the Peripheral Rotablator PRO and "Rotablator PRO." Omitted data were [redacted] of the advancer/catheter, which is not affected by the difference in the target site between the Peripheral Rotablator PRO and the "Rotablator PRO."

2.(6).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the rationale for the use of the anatomy model of the lower limb vessels.

The applicant's explanation:

The vessel model used in the evaluation mimicked the anatomical condition of [redacted]. The [redacted] model was used in [redacted], constructed based on [redacted] from [redacted] individuals. [redacted] model is constructed based on [redacted] from [redacted] individuals. Because the Peripheral Rotablator PRO is intended for below-the-knee atherectomy, the model mimics the combined anatomical structure [redacted]

[redacted], which is considered appropriate.

PMDA reviewed the product performance data and concluded that there were no particular problems including the validity of the vessel models used for evaluation.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the product to the Essential Principles.

(1) The conformity of the product to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," essential elements to balance the risks and benefits of the product are the selection of eligible patients as well as the provision of training for healthcare professionals and compliance with the proper use guidelines prepared in collaboration with the relevant academic societies. Accordingly, it was decided that approval conditions should be attached to ensure that these necessary measures are implemented.

(2) The conformity of the product to Article 2, which stipulates risk management throughout the life cycle of medical device:

PMDA's view:

As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," in Japan, there are limited clinical data for the evaluation of the efficacy and safety of the product. It is considered necessary to evaluate efficacy and safety in clinical use in Japan, and take additional risk minimization measures as necessary. Therefore, PMDA instructed the applicant to conduct a use-results survey.

(3) The conformity of the product to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices:

PMDA's view:

As described earlier in Section "2.(6).B Outline of the review conducted by PMDA," the performance of the Peripheral Rotablator PRO was validated. As described later in Section "6.B Outline of the review conducted by PMDA," based on the results from the clinical study, it is considered that the product can be used effectively and safely when used in eligible patients by carefully selected physicians with a thorough understanding and experience in the procedures using the product. Therefore, PMDA concluded that there were no problems with conformity to Articles 3 and 6.

(4) The conformity of the product to Article 4, which stipulates the term of validity or lifetime of medical devices:

PMDA's view:

As described earlier in Section "2.(5).B Outline of the review conducted by PMDA," the applicant submitted a self-declaration stating that the shelf life for the product was selected after the required stability evaluation was performed in accordance with the "Handling of Stability Studies Related to the Determination of the Shelf life in the Application for Marketing Approvals (Certifications) of Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). Therefore, PMDA concluded that there were no problems with conformity to Article 4.

(5) The conformity of the product to Article 8, which stipulates the prevention of microbial contamination of medical devices:

PMDA's view:

As described later in Section "5.B Outline of the review conducted by PMDA," the adequacy of the Peripheral Rotablator PRO was demonstrated in the prevention of microbial contamination and therefore, there were no problems with conformity to Article 8.

(6) The conformity of the product to Article 13, which stipulates considerations for active medical devices, and to Article 14, which stipulates considerations for mechanical risks of medical devices:

PMDA's view:

As described earlier in Section "2.(6).B Outline of the review conducted by PMDA," and later in Section "4.B Outline of the review conducted by PMDA," the adequacy of the Peripheral Rotablator PRO was demonstrated in the considerations for active medical devices and mechanical risks of medical devices. Therefore, there were no problems with conformity to Articles 13 and 14.

(7) The conformity of the product to Article 17, which stipulates Information on Precautions, etc.:

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," to maintain

the risk-benefit balance of the product, it is important that eligible patients are selected by physicians with sufficient knowledge and experience in diagnosing and treating CLTI, and that the Peripheral Rotablator PRO is used only after becoming fully familiar with its characteristics. Relevant information should be disseminated through Information on Precautions, etc., proper use guidelines, training programs, etc.

Based on the above, PMDA concluded that there were no particular problems with conformity of the Peripheral Rotablator PRO to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management implemented for the product, the risk management system, and the progress of implementation in accordance with ISO14971:2019 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management, taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA," and concluded that there were no particular problems.

5. Manufacturing Process

5.A Summary of the data submitted

Data on the manufacturing process were omitted because the manufacturing site, manufacturing process, sterilized packaging, and sterilization method for the product are the same as the advancer/catheter of the "Rotablator PRO."

5.B Outline of the review conducted by PMDA

PMDA concluded that based on the comparability with the advancer/catheter of the "Rotablator PRO," the omission of these data is acceptable.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

For the present application, the applicant submitted the results from the RESCUE-BTK study conducted in patients with CLI in whom balloon angioplasty had failed, which evaluated the safety and efficacy of the "Rotablator," the preceding product as an adjunctive device for balloon angioplasty.

6.A.(1). Study design

The RESCUE-BTK study is a multicenter, investigator-initiated study conducted in 17 patients at 10 study centers in Japan from [redacted] 20[redacted] to [redacted] 20[redacted]. The study aimed to evaluate the safety and efficacy of the preceding product as an adjunctive device for balloon angioplasty in CLI patients in whom previous balloon angioplasty resulted in failure. Eligible CLI patients were those who had undergone unsuccessful pre-trial balloon angioplasty with a target lesion of ≥2 mm to ≤4 mm in reference vessel diameter and <100 mm (per lesion) in length located between the distal popliteal arteries and the distal below-the-knee arteries. Table 6 shows the outline of the clinical study.

Table 6. Outline of the RESCUE-BTK study

Item	Outline
Objectives	To evaluate the safety and efficacy of the preceding device (Rotablator) as an adjunctive device in balloon angioplasty in patients with CLI who underwent unsuccessful balloon angioplasty
Design	Prospective, non-randomized, multicenter
Sample size	17 patients (full registration)
Summary of key inclusion criteria	Provisional registration (1) Patients with CLI due to atherosclerotic LEAD classified Rutherford category 4 or 5 (2) Skin perfusion pressure (SPP) ≤50 mmHg below the ankle joint of the affected limb (3) Patients with at least 1 of the following factors: - Diabetes mellitus: definitive diagnosis confirmed by the physician - Maintenance dialysis: hemodialysis or peritoneal dialysis - Renal failure: eGFR <60 mL/min/1.73 m^2 - Aged ≥65 years - Radiographically confirmed calcification in below-the-knee arteries of the affected limb Full registration (1) Unsuccessful pre-trial balloon angioplasty, defined as balloon uncrossable (≥75% residual stenosis) within 2 weeks before the full registration (2) Patients presenting with calcification in the target lesion (3) Patients presenting with target lesion between the distal popliteal artery and the distal crural artery[1] (4) Patients with target lesion with a reference vessel diameter[2] of ≥2 mm to ≤4 mm (5) Patients with target lesion length <100 mm (per lesion)[3] (for the case of vascular occlusion, patients with lesion length of <100 mm identifiable by peripheral contrast agent via collateral flow) [1.] Dorsalis pedis artery and plantar artery are excluded. [2.] The reference vessel diameter is defined as the inner diameter of normal vessel of the distal lesion. [3.] Lesion length is measured using a ruler or based on balloon length.
Summary of key exclusion criteria	Provisional registration (1) Patients with prior bypass surgery in crural artery of the affected limb (2) Patients with stent implanted in target vessel (3) Patients with prior endovascular intervention in non-target vessel of the affected limb within 1 week before registration (regardless of success/failure) (4) Abnormal result in any of the following laboratory test at screening: 1) Platelet count <8.0 × 10^4/mL or ≥60.0 × 10^4/mL 2) White blood cell count <3,000/mL 3) Hemoglobin <8.0 g/dL (5) Patients who, in judgement of the investigator, have a life expectancy of <1 year Full registration (1) Patients with occlusive lesion through which a guidewire cannot pass (2) Patients with angiographically confirmed thrombus
Primary endpoint	Success rate of balloon angioplasty after the trial procedure * Success of balloon angioplasty was defined as meeting the following 3 requirements based on the

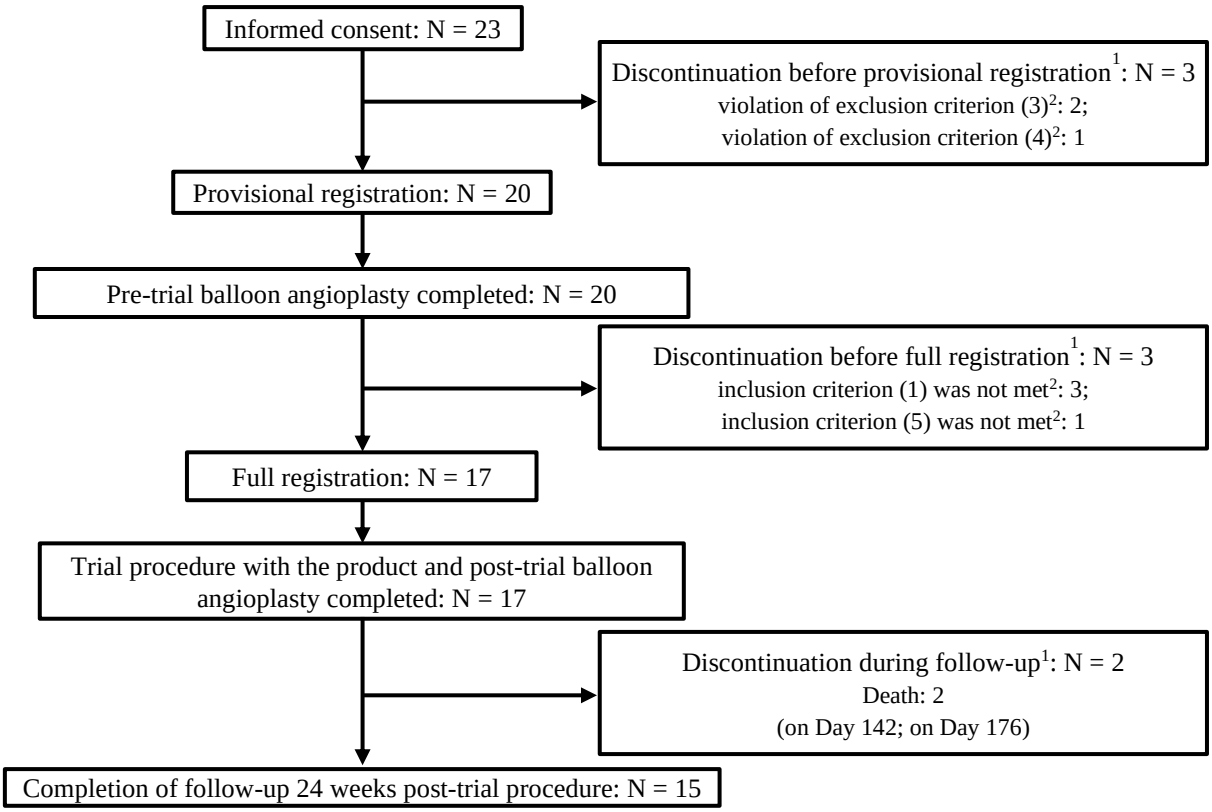
	assessment by the core laboratory: • Residual stenosis <50%[1] • No delayed flow[2] and vessel perforation in the target vessel • Securing antegrade flow to the foot [1.] If both visual evaluation and quantitative angiographic analysis indicate <50%. [2.] Delayed flow is defined as a new occurrence of delayed flow of angiographic contrast agent observed after the procedure. However, for patients with a pre-procedural occlusive lesion, the definition of procedural success does not include delayed flow, and if additional treatment resolves the delay, it should be considered that there is no delayed flow.
Secondary endpoints	**Efficacy evaluation** • Change in the degree of stenosis of target lesion as assessed by quantitative angiographic analysis • Limb salvage rates for the affected limb • Major amputation-free survival • Change from baseline in visual analog scale score (VAS) • Change in ankle-brachial index (ABI) of the affected limb • Change in SPP of the affected limb • Distribution of Rutherford classification categories and their changes • Wound assessment • Residual stenosis (%) by visual assessment at the final confirmatory angiography (on-site evaluation) • Balloon catheter crossing rate (cases of balloon uncrossable lesions in the pre-trial procedure) **Safety evaluation** • Number of distal embolizations[1] after the trial procedure (up to 5 days after trial procedure) • Number of re-occlusions[2] after the trial procedure • Number of total deaths • Number of cardiovascular events[3] • Number of re-interventions[4] for the target vessel of trial procedure [1.] Distal embolization: distal embolization was considered to have occurred when both of the following were visually confirmed: (1) worsening of the color tone of the foot, or emergence of new necrosis; (2) when re-occlusion is radiographically ruled out. [2.] Re-occlusion: occlusion of the target lesion site confirmed by angiography or lower limb ultrasonography. [3.] Cardiovascular event: defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or transient ischemic attack. [4.] Re-intervention: defined as intervention performed in the target vessel during the trial procedure.

The primary endpoint was “the procedural success rate of balloon angioplasty after the trial procedure,” defined as meeting 3 requirements in the assessment by the core laboratory: (1) residual stenosis of <50% (visual and quantitative angiographic analysis); (2) absence of delayed flow of contrast agent and vessel perforation in the target vessel; and (3) securing antegrade flow to the foot. This study was to be conducted in patients in whom the balloon angioplasty success rate would be 0% if without using the product. Assuming a clinically relevant value of 50% as the pre-specified success rate for the primary endpoint and 85% as the target success rate, a sample size of 17 patients was required for attaining a power of at least 80% at a significance level of 2.5%. If ≥13 of 17 patients had successful balloon angioplasty after the trial procedure, the null hypothesis was to be rejected, and the trial procedure was deemed to be successful.

In this study, the primary endpoint and secondary efficacy endpoints were analyzed in the primary analysis population, defined as patients enrolled in the study who underwent the trial procedure, had at least one of the efficacy endpoints measured at any time before or after the procedure, and had pre-trial balloon angioplasty determined as unsuccessful based on the core laboratory assessment. The analyses for secondary endpoints (safety) involved all patients enrolled in the

study who underwent the trial procedure.

Figure 2 shows the flow chart of the clinical study. In this study, informed consent was obtained from 23 patients, and 20 patients were provisionally registered. Of the 20 patients, 3 patients were excluded because the pre-trial procedure balloon angioplasty performed within 2 weeks prior to the full registration did not meet the failure criteria, and therefore these patients were not enrolled. All of the 17 fully registered patients completed the trial procedure with the product and the following balloon angioplasty. Two patients died before completing the 24-week follow-up period after the procedure, and 15 patients completed the 24-week follow-up period after the procedure.



[1.] Total number of patients; [2.] Number of patients by reason (multiple choices)

Figure 2. Flow diagram of RESCUE-BTK study

6.A.(2) Patient characteristics

The patient characteristics, data on lesions at the time of pre-trial balloon angioplasty, and target lesion characteristics are presented in Table 7, Table 8, and Table 9, respectively.

Table 7. Patient characteristics

Category	Percentage (n/N)
Sex	
Male	76.5% (13/17)
Female	23.5% (4/17)
Age (years) Mean ± standard deviation (Min, median, Max)	74.1 ± 8.3 (54, 74.0, 90)
Risk factors	
Smoking history: Yes	70.6% (12/17)
Hypertension	88.2% (15/17)
Dyslipidemia	76.5% (13/17)
Diabetes mellitus	58.8% (10/17)
Medical history	
Maintenance dialysis (present)	76.5% (13/17)
Coronary angioplasty (past, present)	47.1% (8/17)
Coronary artery bypass grafting (past)	5.9% (1/17)
Heart failure hospitalization (past, present)	17.6% (3/17)
Estimated glomerular filtration rate (eGFR) Mean ± standard deviation (Min, median, Max)	21.23 ± 29.13 (4.3, 5.80, 83.3)
Catheter treatment: Yes	70.6% (12/17)
Aorta	8.3% (1/12)
Iliac artery right/left	8.3% (1/12) / 8.3% (1/12)
Femoral-popliteal artery right/left	33.3% (4/12) / 50.0% (6/12)
Below-the-knee artery right/left	50.0% (6/12) / 66.7% (8/12)
Bypass surgery: Yes	0.0% (0/17)
Amputation: Yes	23.5% (4/17)
Minor amputation: affected limb/contralateral limb	0.0% (0/4) / 75.0% (3/4)
Major amputation: contralateral above the knee/contralateral below the knee	25.0% (1/4) / 0.0% (0/4)
Rutherford classification 4/5	29.4% (5/17) / 70.6% (12/17)
Measured ABI of affected limb Mean ± standard deviation (Min, median, Max)	0.906 ± 0.245 (0.57, 0.840, 1.50)
Dorsum of foot SPP (mmHg) Mean ± standard deviation (Min, median, Max)	33.5 ± 14.3 (13, 31.0, 70)
Plantar region SPP (mmHg) Mean ± standard deviation (Min, median, Max)	38.1 ± 21.5 (10, 34.5, 79)
Wound: Yes	70.6% (12/17)

Table 8. Data on lesions at the time of pre-trial procedure balloon angioplasty

Category	Percentage (n/N)
Percent stenosis by visual estimation ≥75% (assessment by core laboratory)	100.0% (17/17)
Target lesion site	
Popliteal artery	5.9% (1/17)
Tibioperoneal trunk	0.0% (0/17)
Anterior tibial artery	52.9% (9/17)
Posterior tibial artery	23.5% (4/17)
Peroneal artery	17.6% (3/17)
Target lesion length (assessment by core laboratory) Mean ± standard deviation (Min, median, Max)	60.8 ± 26.9 (14, 70.0, 96)
Antegrade flow to foot (assessment by core laboratory) Yes/No	88.2% (15/17) / 11.8% (2/17)
Angiography (lesion length) (assessment by medical institution)[1] Mean ± standard deviation (Min, median, Max)	55.4 ± 29.5 (15, 50.0, 99)
Angiography (reference vessel diameter) (assessment by medical institution)[1] Mean ± standard deviation (Min, median, Max)	2.70 ± 0.50 (2.0, 2.50, 4.0)

[1.] Measured value before procedure

Table 9. Target lesion characteristics

Patient No.	Lesion	Target lesion (assessment by medical institution)[2]				
		Location of lesion (detail)[1]	Localized/diffuse calcified lesion	Eccentric/circumferential calcified lesion	Tortuosity	New/ restenosis
1	Proximal	Anterior tibial artery (AT3)	Diffuse	Circumferential	None	New
2	Proximal	Anterior tibial artery (AT3)	Diffuse	Circumferential	None	New
3	Proximal	Peroneal artery (Pero1/2)	Diffuse	Circumferential	None	Restenosis
4	Proximal	Anterior tibial artery (AT1/2)	Localized	Circumferential	None	New
5	Proximal	Anterior tibial artery (AT3)	Diffuse	Circumferential	None	Restenosis
6	Proximal	Posterior tibial artery (PT2)	Localized	Circumferential	None	Restenosis
7	Proximal	Peroneal artery (Pero1)	Diffuse	Non-evaluable	None	New
8	Proximal	Anterior tibial artery (AT3)	Diffuse	Circumferential	None	Restenosis
9	Proximal	Anterior tibial artery (AT2)	Diffuse	Circumferential	None	New
10	Proximal	Posterior tibial artery (PT1)	Diffuse	Circumferential	None	Restenosis
11	Proximal	Popliteal artery (P3)	Diffuse	Circumferential	None	Restenosis
	Distal	Anterior tibial artery (AT2)	Diffuse	Circumferential	None	Restenosis
12	Proximal	Posterior tibial artery (PT1)	Diffuse	Circumferential	None	New
13	Proximal	Peroneal artery (Pero1)	Diffuse	Circumferential	None	New
14	Proximal	Posterior tibial artery (PT2)	Diffuse	Circumferential	None	New
	Distal	Posterior tibial artery (PT2)	Localized	Circumferential	None	New
15	Proximal	Anterior tibial artery (AT2)	Diffuse	Non-evaluable	None	New
16	Proximal	Anterior tibial artery (AT2)	Diffuse	Circumferential	None	New
17	Proximal	Anterior tibial artery (AT2/3)	Non-evaluable	Circumferential	None	Restenosis

[1.] Popliteal artery: divided into 3 segments (from proximal to distal), P1, P2, and P3; anterior tibial artery: AT1 comprises the ostium to the first bend, and the remaining segment is divided into 2 equal segments, AT2 and AT3 (from proximal to distal); peroneal artery: divided into 2 equal segments, Pero1 and Pero2 (from proximal to distal); posterior tibial artery: divided into 2 equal segments, PT1 and PT2 (from proximal to distal); multiple lesions are included.
[2.] Additional data obtained from the medical institutions

6.A.(3) The procedures in the study

Table 10 summarizes the trial procedure using the product. Table 11 shows the data on balloon angioplasty.

Table 10. Trial procedure using the product

	Percentage (n/N)
Burr size (mm) (may be counted more than once)	
1.25	64.7% (11/17)
1.50	52.9% (9/17)
1.75	0.0% (0/17)
2.00	5.9% (1/17)
2.25	0.0% (0/17)
2.50	0.0% (0/17)
Duration of use (sec) Mean ± standard deviation (Min, median, Max)	94.8 ± 138.8 (10, 50.0, 600)
Max rotational speed (rpm) Mean ± standard deviation (Max, median, Min)	177117.6 ± 10664.7 (150000, 180000.0, 200000)

Table 11. Data on balloon angioplasty

	Pre-trial procedure	Post-trial procedure
Max balloon diameter (mm) Mean ± standard deviation (Min, median, Max)	2.35 ± 0.39 (2.0, 2.50, 3.0)	2.65 ± 0.52 (2.0, 2.50, 4.0)
Balloon length at Max balloon diameter (mm) Mean ± standard deviation (Min, median, Max)	121.8 ± 68.7 (20, 100.0, 250)	153.53 ± 71.23 (20.0, 200.00, 250.0)

6.A.(4) Study results

6.A.(4).1) Primary endpoint

In this study, 17 patients in whom pre-trial procedure balloon angioplasty was unsuccessful as assessed by the core laboratory were analyzed for the primary endpoint “the procedural success rate of balloon angioplasty after the trial procedure” (Table 12). The results show that the procedural success rate was 94.1% (16 of 17 patients) (95% confidence interval, 71.3%-99.9%), indicating that the pre-specified success rate (50%) was met.

One patient (patient No. 13) in whom the primary endpoint was not achieved was due to not meeting the requirement regarding delayed flow of contrast agent[a] at the final confirmatory angiography following post-trial balloon angioplasty, as assessed by the core laboratory. Delayed flow was noted in another patient (patient No. 17); however, since this patient had a total occlusion

[a] Presence of delayed flow: angiographic analysis shows slower flow in the target vessel compared to the non-target vessel (reference vessel) in the same image.
Absence of delayed flow: angiographic analysis shows the flow speed of the target vessel is comparable to that of the non-target vessel (reference vessel) in the same image. (For the assessment of new emergence or worsening of delayed flow, pre-trial procedure findings are also used for comparison)

before the trial procedure (100.0% stenosis by quantitative angiographic analysis before trial procedure as assessed by the core laboratory), the delayed flow did not meet the study's definition of "unsuccessful procedure." Therefore, the requirements for meeting the primary endpoint were considered to have been met.

Table 12. Summary of data on trial procedure in each patient

Patient No.	Pre-trial procedure[1]		At trial procedure[2]		Final confirmatory angiography after balloon angioplasty[1]					
	Presence of antegrade flow	Stenosis (%)	Reference vessel diameter (mm)	Lesion length (mm)	Stenosis(%)	Presence of delayed flow	Vessel perforation	Presence of antegrade flow	Distal embolization	Vessel dissection
1	Yes	47.5	2.5	70	29.7	No	No	Yes	No	No
2	Yes	60.6	2.5	50	23.2	No	No	Yes	No	No
3	Yes	49.8	3.0	30	12.1	No	No	Yes	No	No
4	Yes	63.0	3.0	70	26.9	No	No	Yes	No	有
5	Yes	46.5	3.0	45	19.9	No	No	Yes	No	No
6	Yes	69.0	3.0	30	42.5	No	No	Yes	No	No
7	No	100.0	2.4	40	14.5	No	No	Yes	Undeterminable No images	No
8	Yes	58.7	2.5	98	31.8	No	No	Yes	No	No
9	Yes	78.4	2.5	99	20.2	No	No	Yes	No	No
10	Yes	67.9	2.5	90	37.9	No	No	Yes	No	No
11[3]	Yes	68.6	4.0	15	19.0	No	No	Yes	No	No
	Yes	60.9	2.5	90	21.3	No	No	Yes	No	No
12	Yes	50.1	2.0	80	13.7	No	No	Yes	No	No
13	Yes	54.0	3.5	80	28.7	Yes	No	Yes	Undeterminable Images available	No
14[3]	Yes	43.5	2.0	20	21.2	No	No	Yes	No	Yes
	Yes	49.8	2.0	20	20.5	No	No	Yes	No	No
15	Yes	50.1	2.5	25	24.0	No	No	Yes	No	Yes
16	Yes	55.8	2.5	20	19.7	No	No	Yes	No	No
17	No	100.0	2.5	80	19.3	Yes	No	Yes	Yes	No

[1]. Assessment by the core laboratory
[2]. Assessment by the medical institution
[3]. Proximal lesion (upper row), distal lesion (lower row)

6.A.(4).2) Secondary endpoints (efficacy evaluation)

The quantitative angiographic analysis showed the stenosis of the target lesion (assessment by the core laboratory) as 62.56 ± 16.99% pre-trial procedure, 43.73 ± 16.76%[b] after the use of the product, and 23.78 ± 8.30% at the final confirmatory angiography. The pre-trial procedure percent stenosis of the target lesion tended to decrease with stages after the procedure.

No major amputations were reported at 24 weeks post-trial procedure, with a limb salvage rate of 100.0%.

Pain was evaluated using a VAS. The baseline mean VAS score was 31.1 ± 24.3 mm, which improved to 19.9 ± 18.2 mm on the day following the trial procedure, 16.2 ± 17.6 mm at 4 weeks

[b] Data from 16 patients. Data for 1 patient whose core laboratory assessment post-trial procedure (before balloon angioplasty) was "undeterminable, images available" were excluded.

post-trial procedure, 25.0 ± 28.6 mm at 12 weeks post-trial procedure, and 19.3 ± 28.7 mm at 24 weeks post-trial procedure, indicating that the improvement was maintained.

The mean ABI of the affected limb, 0.906 ± 0.245 at baseline, was improved to 1.020 ± 0.282 on the day following the trial procedure and 1.036 ± 0.238 at 4 weeks post-trial procedure. However, the mean ABI showed no improvement compared to baseline, 0.832 ± 0.183 and 0.806 ± 0.176 at 12 weeks and 24 weeks post-trial procedure, respectively.

The mean dorsum of foot SPP and the mean plantar region SPP of the affected limb were 33.5 ± 14.3 mmHg and 38.1 ± 21.5 mmHg, respectively, at baseline, and improvement was maintained compared to baseline: 49.5 ± 25.4 mmHg and 46.3 ± 17.3 mmHg, respectively, on the day following the trial procedure, 51.5 ± 15.7 mmHg and 54.9 ± 21.6 mmHg, respectively, at 4 weeks post-trial procedure, 44.1 ± 21.2 mmHg and 50.8 ± 27.1 mmHg, respectively, at 12 weeks post-trial procedure, and 41.1 ± 23.9 mmHg, 47.7 ± 21.5 mmHg, respectively, at 24 weeks post-trial procedure (Table 13).

Table 13. Change in SPP of affected limb

Item		Baseline	Day following the trial procedure	4 weeks post-trial procedure	12 weeks post-trial procedure	24 weeks post-trial procedure
Dorsum of foot	N	15	17	17	16	14
	Mean (mmHg)	33.5	49.5	51.5	44.1	41.1
	SD	14.3	25.4	15.7	21.2	23.9
	Median (Min, Max)	31.0 (13, 70)	48.0 (12, 125)	45.0 (30, 79)	39.5 (17, 89)	39.5 (3, 87)
Plantar region	N	16	17	17	16	14
	Mean (mmHg)	38.1	46.3	54.9	50.8	47.7
	SD	21.5	17.3	21.6	27.1	21.5
	Median (Min, Max)	34.5 (10, 79)	46.0 (18, 73)	53.0 (22, 90)	41.5 (11, 113)	48.5 (7, 82)

At baseline, 29.4% (5 of 17) of patients were classified as Rutherford category 4, 70.6% (12 of 17) of patients were classified as Rutherford category 5. At 4 weeks after the trial procedure, 35.4%, 11.8%, and 52.9% of patients were classified as Rutherford category ≤3, category 4, and category 5, respectively; at 12 weeks after the trial procedure, 41.2%, 11.8%, and 47.1% of patients were classified as Rutherford category ≤3, category 4, and category 5, respectively; at 24 weeks after the trial procedure, 35.3%, 11.8%, 35.3%, and 5.9% of patients were classified as Rutherford category ≤3, category 4, category 5, and category 6, respectively, indicating that the improvement was maintained for up to 24 weeks post-trial procedure (Table 14).

Table 14. Change in Rutherford classification

Category[1]	Baseline	4 weeks post-trial procedure	12 weeks post-trial procedure	24 weeks post-trial procedure
0	0.0% (0/17)	11.8% (2/17)	17.6% (3/17)	29.4% (5/15)
1	0.0% (0/17)	11.8% (2/17)	5.9% (1/17)	0.0% (0/15)
2	0.0% (0/17)	5.9% (1/17)	5.9% (1/17)	0.0% (0/15)
3	0.0% (0/17)	5.9% (1/17)	11.8% (2/17)	5.9% (1/15)
4	29.4% (5/17)	11.8% (2/17)	11.8% (2/17)	11.8% (2/15)
5	70.6% (12/17)	52.9% (9/17)	47.1% (8/17)	35.3% (6/15)
6	0.0% (0/17)	0.0% (0/17)	0.0% (0/17)	5.9% (1/15)

[1.] Rutherford categories are clinically defined as follows:
Category 0, asymptomatic—no hemodynamically significant occlusive disease; Category 1, mild claudication; Category 2, moderate claudication; Category 3, severe claudication; Category 4, ischemic rest pain; Category 5, minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia; Category 6, major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable

In this study, a total of 18 wounds were observed in 12 patients at baseline. At 24 weeks after the trial procedure, the proportion of patients with 0 wounds was 50% (6 of 12 patients) and the proportion of healed wounds was 66.7% (12 of 18 wounds). Both the proportion and number of wounds decreased after the trial procedure compared to baseline, and wounds improved compared to pre-trial procedure levels (Table 15).

Table 15. Wound data for each patient (assessment by the medical institution)

Patient No.	Wound No.	Post-trial procedure (days)	Site	Lesion depth	Size (mm^2)	Wound type	Infection	Outcome at final evaluation[1] (days post-trial procedure)
1	1	-3	Hallux	Subcutaneous tissue	50	Ulcer	No	Healed (75)
	2	-3	Hallux	Skin loss	42	Ulcer	No	Healed (33)
2	1	-3	Second toe	Subcutaneous tissue	640	Ulcer necrosis	No	Healed (72)
3	1	-2	Fourth toe	Skin loss	9	Ulcer	No	Healed (29)
	2	29	Fourth toe	Skin loss	25	Ulcer	No	Healed (98)
	3	98	Third toe	Skin loss	200	Ulcer	No	Unknown outcome[2]
4	1	1	Hallux	Skin loss	750	Ulcer necrosis	No	Wound size: increased; lesion depth: tendon or bone exposure (155)
	2	155	Foot (exc. toes/heel)	No loss	225	Ulcer	No	Continued (155)
7	1	-6	Fifth toe	Skin loss	204	Necrosis	No	Healed (174)
8	1	-3	Hallux	Tendon or bone exposure	500	Ulcer necrosis	Yes	Wound size: decreased; lesion depth: subcutaneous tissue (144)
	2	26	Second toe	Subcutaneous tissue	35	Ulcer	No	Wound size: increased (144)
9	1	-1	Heel	Subcutaneous tissue	105	Ulcer	No	Healed (24)
	2	-1	Fifth toe	Subcutaneous tissue	25	Ulcer necrosis	No	Healed (87)
11	1	-5	Foot (exc. toes/heel)	Skin loss	Unknown	Ulcer	No	Healed (28)
	2	-5	Second toe	Skin loss	Unknown	Necrosis	No	Healed (84)
	3	-5	Third toe	Skin loss	Unknown	Ulcer	No	Healed (84)
12	1	-2	Hallux	Subcutaneous tissue	25	Ulcer necrosis	No	Wound size: decreased (149)
	2	-2	Hallux	Skin loss	2200	Ulcer	No	Healed (28)
13	1	-2	Fourth toe	Subcutaneous tissue	4	Ulcer	Yes	Wound size: decreased; lesion depth: tendon or bone exposure (142)
14	1	-3	Heel	Subcutaneous tissue	108	Ulcer necrosis	No	Healed (156)
15	1	-3	Hallux	Skin loss	85	Ulcer necrosis	No	Wound size: increased (77)[3]
	2	-3	Fifth toe	Skin loss	450	Ulcer necrosis	No	Wound size: decreased; lesion depth: tendon or bone exposure (77)[3]
17	1	184	Hallux	Subcutaneous tissue	40	Ulcer	No	Continued (184)

[1.] For healed wound, the number of days post-trial procedure until healing was confirmed. If there was no change in lesion depth, description on lesion depth was omitted.
[2.] Because the patient died at 142 days after the trial procedure, there are no wound evaluation data at 24 weeks post-trial procedure.
[3.] Because the patient died at 176 days after the trial procedure, there are no wound evaluation data at 24 weeks post-trial procedure.

The mean EQ-5D-5L quality of life (QOL) score was 0.5542 ± 0.2162 at baseline, increased to 0.6512 ± 0.2066 at 4 weeks post-trial procedure, and 0.6102 ± 0.1916 and 0.6030 ± 0.2254 at 12

weeks and 24 weeks post-trial procedure, respectively. The mean EQ-5D-5L health status score was 59.4 ± 20.6 at baseline, increased to 66.9 ± 19.5 at 4 weeks post-trial procedure, and 61.8 ± 20.7 and 67.3 ± 21.6 at 12 weeks and 24 weeks post-trial procedure, respectively, indicating that improvement in QOL and health status was maintained.

6.A.(4).3) Secondary endpoints (safety evaluation)

In this study, the incidence of any adverse events up to 24 weeks post-trial procedure was 88.2% (15 of 17 patients). The incidence of adverse events for which a causal relationship to the trial device could not be ruled out was 23.5% (4 of 17 patients), the incidence of adverse events for which a causal relationship to the trial procedure could not be ruled out was 23.5% (4 of 17 patients). The incidence of serious adverse events was 52.9% (9 of 17 patients), and 17 events were reported in 9 patients. The incidence of adverse events (serious or non-serious) for which a causal relationship to the trial device or trial procedure could not be ruled out was 23.5% (4 of 17 patients), and 7 events reported in 4 patients are presented in Table 16.

Table 16. Adverse events for which a causal relationship to the trial device or trial procedure could not be ruled out

Patient No.	Number of days after trial procedure	Adverse event	Serious/non serious	Additional procedure	Outcome
1	1	Device breakage	Non-serious	None	Not resolved
	6	Chondrocalcinosis pyrophosphate	Serious	None	Resolved
	126	Peripheral ischemia	Serious	Re-intervention in target vessel	Resolving
6	78	Peripheral arterial obstruction	Serious	Re-intervention in target vessel	Not resolved[1]
8	68	Peripheral artery restenosis	Serious	Re-intervention in target vessel	Resolved
	145	Peripheral artery restenosis	Serious	Re-intervention in target vessel	Resolved
16	94	Peripheral ischemia	Serious	Re-intervention in target vessel	Resolved

[1.] Balloon angioplasty was performed on the target vessel multiple times after the 24th week post trial-procedure. Subsequently, the patient was discharged from the hospital, with resolving condition (additional data obtained from the medical institution).

No distal embolization occurred in any of the 17 patients up to 5 days after the trial procedure based on the assessment by the medical institution.

Up to 24 weeks after the trial procedure, re-occlusion occurred in 5 of 13 patients (38.5%) (95% CI, 13.9%-68.4%). Of the 17 patients, re-angiography was not performed in 2 patients who died, 1 patient, in whom lower limb ultrasonography was not possible due to a wound in the affected limb, refused to undergo examination at the time of re-angiography, another patient underwent re-angiography but the result was undeterminable by the core laboratory assessment. After these

patients were excluded, a total of 13 patients were evaluable for re-occlusion. Re-intervention in the target vessel was performed in 6 of 17 patients (35.3%) (95% CI, 14.2%-61.7%) up to 24 weeks after the trial procedure (Table 17). Of the 5 patients who experienced re-occlusion, 4 patients had undergone re-intervention, and in the remaining 1 patient, re-occlusion was confirmed at the re-angiography at 24 weeks post-trial procedure. For all the cases of re-intervention, balloon angioplasty was performed.

Table 17. Re-intervention in target vessel up to 24 weeks post-trial procedure

Patient No.	Number of days after trial procedure	Reason (wound)	Reason (pain)	Reason (SPP)	Number of treated lesions	Target lesion at the trial procedure	% stenosis (before re-intervention)[1]	% stenosis (after re-intervention)[1]
1	126	Recurrence	Recurrence	Subsequent decrease	1	Included	100.0	39.7
4	155	Worsening	No change	Subsequent decrease	1	Included	54.7	24.1
6	132	No change	Recurrence	Subsequent decrease	1	Included	100.0	40.1
8	68	Worsening[2]	No change	No change	1	Included	57.9	24.0
	145	No change	No change	Subsequent decrease	1	Included	40.7	23.3
16	107	No change	Recurrence	Not performed	1	Included	100.0	Undeterminable
17	190	New	New	Subsequent decrease	1	Included	100.0	39.8

[1.] Assessment by the core laboratory
[2.] Originally, there was a diffuse calcified lesion, and ulcer also developed on the second toe; therefore, the re-intervention was performed.

Up to 24 weeks after the trial procedure, 2 of 17 patients (11.8%) (95% CI, 1.5%-36.4%) died (ischemic cardiomyopathy on the 142nd day post-trial procedure, and pneumonia on the 176th day post-trial procedure). Causal relationships to the trial device and trial procedure were ruled out for both cases based on the assessment conducted by the medical institution. A cardiovascular event occurred in 1 of 17 patients (5.9%, cardiovascular death) (95% CI, 0.1%-28.7%).

Malfunctions were reported in 2 of 17 patients (11.8%). By category, malfunctions of guidewires were “guidewire fracture, retained fragments” (11.8%, 2 of 17 patients), malfunctions of burrs included “burr not working properly on guidewire” (5.9%, 1 of 17 patients) and “rotational speed instability” (5.9%, 1 of 17 patients). No console malfunctions were reported.

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning of Peripheral Rotablator PRO

The applicant’s explanation about the clinical positioning of the Peripheral Rotablator PRO:
Currently, surgical bypass or classic balloon angioplasty are the options for revascularization of below-the-knee artery lesions in Japan. In practice, treatment is selected according to the patient’s general condition and life expectancy; however, for patients in whom no autogenous veins are

available for grafting or no suitable anastomotic sites are available for a surgical bypass procedure, balloon angioplasty is the only option for below-the-knee arterial lesions. In Japan, it has been reported that in below-the-knee arterial lesions in patients with CLTI, balloon angioplasty was unsuccessful in 5.8% of patients not on dialysis and 12.3% of those on dialysis,[8] and the procedural success rate of balloon angioplasty was 93.3% according to a meta-analysis of clinical studies.[12] These reports suggest that balloon angioplasty for revascularization fails in approximately 10% of patients. Consequently, these patients will receive conservative treatment, undergo major amputation, or will be placed under observation without the possibility of undergoing major amputation. Given these circumstances, there is a high medical need for the product, which enables successful balloon angioplasty in patients in whom balloon angioplasty for below-the-knee arterial lesions was previously unsuccessful.

PMDA's view:
In Japan, approximately 70% to 80% of patients with CLTI have diabetes mellitus, and approximately 50% of patients with CLTI are on dialysis. Calcification is common in vascular lesions in patients with diabetes mellitus or on dialysis, and these lesions are characterized by severe calcification extending from below-the-knee arteries to foot arteries.[3] For below-the-knee lesions in patients with CLTI who require revascularization, endovascular treatment (balloon angioplasty) is generally selected for limb salvage, pain relief, and wound healing when surgical revascularization is not feasible. Therefore, as explained by the applicant, the Peripheral Rotablator PRO enables successful balloon angioplasty for patients for whom it was previously unsuccessful. When the risks are clinically acceptable, it is useful to introduce the product into clinical practice.

6.B.(2) Endpoints and targets for the clinical study

The applicant's explanation about the rationale for the selection of the primary endpoint and the appropriateness of the targets set for the clinical study:
The primary endpoint for the RESCUE-BTK study is the procedural success rate of balloon angioplasty after the trial procedure (success is defined as residual stenosis <50% after balloon angioplasty after the trial procedure). This was determined based on recommendations included in the consensus definitions[13] regarding the evaluation and treatment of peripheral arterial occlusive disease released by the Peripheral Academic Research Consortium in 2015, i.e., lesion diameter stenosis ≥50% was eligible for recanalization; and procedural success was defined as residual diameter stenosis ≤50% after revascularization.

The success rate of balloon angioplasty was assumed to be 0% without using the product in patients with previously unsuccessful balloon angioplasty as control population. When balloon

angioplasty performed using the product as an adjunctive device met the definition of procedural success (residual diameter stenosis ≤50%) in 50% of patients, that was considered clinically significant and appropriate.

PMDA's view:
The endpoints proposed for the clinical study are acceptable based on the following factors:

- The primary endpoint "the procedural success rate of balloon angioplasty after the trial procedure" assesses whether balloon angioplasty can be completed without delayed flow or vessel perforation by using the product for calcified below-the-knee lesions for which balloon angioplasty was unsuccessful, thereby achieving revascularization.
- Secondary endpoints include the limb salvage rate, wound assessment, and the number of target vessel re-interventions at 24 weeks after trial procedure, allowing comprehensive evaluation of the chronic stage outcome of balloon angioplasty with the product as an adjunctive device.

A residual diameter stenosis of <50%, as defined in the criterion "procedural success rate of balloon angioplasty after the trial procedure" in the primary endpoint, is an indicator that has been adopted in some clinical studies conducted in below-the-knee arteries in the past.[14] Therefore, it was concluded that a residual diameter stenosis of <50% is an acceptable target in patients for whom no other treatment options are available.

The applicant's explanation, i.e., the Peripheral Rotablator PRO is clinically positioned as a device for adjunctive use in patients in whom previous balloon angioplasty resulted in failure, and the success rate of the conventional treatment would be 0%, is acceptable. The target proportion of patients fulfilling the primary endpoint requirements, 50%, is considered of a certain level of clinical significance, taking into account the comments in the Expert Discussion. PMDA has concluded that the applicant's explanation is acceptable.

6.B.(3) Efficacy and safety

6.B.(3).1) Efficacy

Based on the results of the primary endpoint, the prespecified target was met, and thus the results demonstrated the efficacy of the product. However, as an atherectomy device, the product must also support revascularization with clinically acceptable risks. PMDA asked the applicant to explain the risks of delayed flow associated with the use of the product, and of distal embolization that can lead to delayed flow, as in the definition in the primary endpoint of the clinical study.

The applicant's explanation:

The patient (patient No. 13), in whom balloon angioplasty was unsuccessful as per the primary endpoint definition, was determined by the medical institution to have experienced distal embolization at the final confirmatory angiography, which was also considered to cause delayed flow. In the same patient, device malfunctions (guidewire fracture, retained fragments) also occurred during the procedure. For this reason, a causal relationship to the malfunction cannot be ruled out for the delayed flow.

In another patient (patient No. 17) in whom delayed flow occurred, the target lesion (anterior tibial artery) was completely occluded on the pre-trial procedure angiography, showing marked delayed flow in both the distal anterior tibial artery and dorsalis pedis artery. After balloon angioplasty following the trial procedure, the delayed flow in the target vessel improved significantly. Conversely, it is suspected that no-flow (distal embolization) in the middle segment of the dorsalis pedis artery observed on the final confirmatory angiography occurred after the trial procedure. The possibility cannot be ruled out that distal embolization occurred in association with the procedure with the product, leading to delayed flow. It should also be noted that the embolism in this patient was not caused by malfunction of the product.

According to the reports of past clinical studies in which balloon angioplasty was performed in patients with CLTI with below-the-knee arterial lesions, delayed flow occurred in 18.6% of patients and distal embolization in 0.4% to 0.6% of patients.[14,15,16] In a meta-analysis study (of the 16 studies analyzed, 12 studies have CLTI patient populations, and all studies include Rutherford category ≥4 patient populations) that compared the outcomes of balloon angioplasty and stent in below-the-knee arterial lesions, the incidence of distal embolization or thrombus after balloon angioplasty for below-the-knee arteries was reported to be 3%.[17] Although direct comparison is difficult because of the differences in procedure and patient population, the incidences of delayed flow (11.8%) and distal embolization (5.9%) in the RESCUE-BTK study were generally comparable, despite some results slightly higher than the results from the clinical studies on balloon angioplasty in CLTI patients with below-the-knee arterial lesions or from the clinical studies on the Rotablator used in coronary or lower extremity arteries.

PMDA view on the efficacy of the product:
Delayed flow was observed in a total of 2 patients (11.8%) on the final confirmatory angiography of the RESCUE-BTK study. These 2 events, which might have been caused by the procedure using the product, should have been classified as unsuccessful balloon angioplasty. Nevertheless, based on the comparison of pre- and post-trial procedure percent stenosis or the primary endpoint results of the study, the product has sufficient ablation capability to contribute to the procedural success in balloon angioplasty for calcified below-the-knee lesions, while keeping the risk of

delayed flow and vessel perforation within the acceptable range. This conclusion was reached with the following reasons:

- The percent stenosis before and after -trial procedure using the product was 62.56 ± 16.99% and 43.73 ± 16.76%, respectively. The percent stenosis in the 2 patients in whom delayed flow was observed was 54.0% and 28.7% pre- and post-trial procedure, respectively in the first patient, and 100% and 19.3% pre- and post-trial procedure, respectively in the second patient, indicating that the percent stenosis decreased when comparing pre- and post-trial procedure levels (Table 12).
- The percent stenosis on the final confirmatory angiography after balloon angioplasty was 23.78 ± 8.30%, indicating a clinically acceptable result.
- If the 2 patients in whom delayed flow was observed on the final confirmatory angiography are classified as unsuccessful cases of balloon angioplasty after the trial procedure, the criterion for the primary endpoint will be met.
- Delayed flow and distal embolization observed in the clinical study did not require additional procedures, and were clinically acceptable events. In addition, no vessel perforation occurred.

The ABI values improved in the 4 weeks following the trial procedure; however, the improved levels were not maintained at 12 weeks and thereafter, and tended to be lower than the baseline. It has been reported that when there are lesions in the arteries below the ankle joint, ABI does not reflect blood flow in the foot,[3] and in patients on dialysis, SPP, which directly assesses the peripheral blood flow in the foot, is the most reliable way to diagnose the severity of ischemia.[18] Therefore, in addition to the results for SPP values, which are assumed to have higher diagnostic utility especially in the patient population of this study, given that other clinical symptom results also show that improvement was maintained at 24 weeks after the trial procedure, hemodynamic improvement was considered acceptable. The effects on wound healing were as follows: of the 12 patients who had wounds at the time of enrollment, wounds in 6 patients (50%) healed. Wounds remained in the other 6 patients, and wounds tended to worsen in 3 patients (patient Nos. 4, 8, and 15) at 4 weeks after the trial procedure. Of the remaining 3 patients, a causal relationship with the product and procedure was ruled out for the wounds in 2 patients in the adverse event reports from the medical institution, while in the remaining 1 patient, the wound was not considered an adverse event. From 26 days to 184 days post-trial procedure, 5 new wounds were identified in a total of 4 patients (patient Nos. 3, 4, 8, and 17) including 1 patient with no wound at baseline. A causal relationship with the product and procedure was ruled out for all wounds in the adverse event reports from the medical institutions. In 3 foreign clinical studies, which evaluated wound healing after balloon angioplasty in below-the-knee arterial lesions in patients with CLTI, the wound healing rate was 46.9% 6 months later and 56.5% to 76.9% 1 year later.[14,19,20] Based on

these data, there is no significant trend towards worsening of wounds when the product was used. It is considered that at 24 weeks after the trial procedure, the wound healing rates were comparable to those for lesions that are treatable without using atherectomy device.

Based on the above, in addition to the results for the primary endpoint, the results for secondary endpoints (efficacy) showed no major amputation of the affected limb at 24 weeks after the trial procedure, maintaining improvements in VAS, SPP (Table 13), Rutherford classification (Table 14), and EQ-5D-5L (QOL, health status), and demonstrated acceptable wound healing. Since clinical symptoms showed a certain level of improvement in by balloon angioplasty using the Peripheral Rotablator PRO as an adjunctive device, PMDA concluded that the clinical efficacy of the product in the patient population of the clinical study was demonstrated.

6.B.(3).2) Safety

6.B.(3).2).(a) Delayed flow, distal embolization, and vascular dissection

In the core laboratory assessment of the final confirmatory angiography in the clinical study, the following events occurred: delayed flow for which a causal relationship to device malfunction cannot be ruled out as well as delayed flow suspected to be due to distal embolization (2 of 17 patients, 11.8%) (Table 18), distal embolization[c] (1 of 17 patients [patient No. 17], 5.9%), and vascular dissection (3 of 17 patients [patient Nos. 4, 14, and 15], 17.6%) (Table 12).

[c] Distal embolization present: occurrence of angiographic no-flow or filling defect in peripheral vessels distal to the target lesion is noted after the procedure.
No distal embolization: no occurrence of angiographic no-flow or filling defect in peripheral vessels distal to the target lesion is noted after the procedure.

Table 18. Detailed information on patients identified with delayed flow on final confirmatory angiography)

Patient No.		13	17
Patient characteristics	Age, sex	7[redacted] years, man	7[redacted] years, woman
	Maintenance dialysis	No	Yes
	SPP (dorsal/plantar)	31/34	27/17
	Wound assessment	1 wound (fourth toe, subcutaneous tissue, 4 mm^2, ulcer, infection)	0 wounds
Pre-trial procedure[1]	Target lesion	Peroneal artery	Anterior tibial artery
	Calcified lesion assessment[5]	Diffuse, circumferential	Diffused or localized is not evaluable; circumferential
	Vessel tortuosity[5]	None	None
	New/restenosis lesion[5]	New lesion	Restenosis lesion
	Lesion length (mm)	80	80
	Reference vessel diameter (mm)	3.5	2.5
	Stenosis (%)	54.0	100.0
	Antegrade flow	Present	Absent
Trial procedure	Burr size	1.50, 1.25	1.50
	Duration of use (sec)	111	15
	Max rotational speed (rpm)	168000	190000
At final confirmatory angiography[2]	Stenosis (%)	28.7	19.3
	Antegrade flow	Present	Present
	Delayed flow	Present	Present
	Distal embolization	Undeterminable, images available	Present
	Vascular dissection	Absent	Absent
Primary endpoint[2]	Balloon angioplasty post-trial procedure	Unsuccessful	Successful
24 weeks post-trial procedure[3]	Stenosis (visual inspection)	<50%	≥50%
	Wound assessment	1 wound (unhealed)	1 wound (hallux, subcutaneous tissue, 40 mm^2, ulcer)[4]
Occurrence of events	Re-intervention (number of days post-trial procedure)	No	Yes (190)
	Re-occlusion (number of days post-trial procedure)	No	Yes (190)
	Device malfunction	Guidewire fracture, retained fragments Burr not working properly on guidewire	No

[1.] Stenosis (%) and antegrade flow were assessed by the core laboratory, and the rest were assessed by the medical institution; [2.] assessment by the core laboratory; [3.] assessment by the medical institution; [4.] new occurrence confirmed 184 days post-trial procedure; [5.] additional data obtained from the medical institutions

The applicant explained whether the risks of delayed flow and distal embolization that can cause delayed flow are acceptable as described earlier in Section "6.B.(3).1) Efficacy." The applicant also explained the cases of 3 patients in whom vascular dissection was confirmed by the core

laboratory assessment on the final confirmatory angiography:

At what stage of the procedure vascular dissection occurred remains unknown, thus the possibility cannot be ruled out that the event could have been due to vessel injury occurring during the use of the product. However, the reported cases were not of severe vascular dissection that could cause vessel perforation, delayed flow, or disruption to antegrade flow to the foot, and did not affect the primary endpoint results. Although the different procedures and patient populations precluded direct comparison, the incidence of vascular dissection in the RESCUE-BTK study was generally comparable, except for the slightly higher percentages of some events in the RESCUE-BTK study than in clinical studies on balloon angioplasty in CLTI patients with below-the-knee arterial lesions[14,15,16,17] and in the clinical studies on the "Rotablator" for coronary or lower extremity arteries (7.5%-19.2%). No device malfunctions occurred in these patients.

PMDA asked the applicant to explain the risk mitigation measures for delayed flow/distal embolization and vascular dissection, which were reported in the study:

The applicant's explanation:
Precautions for product use will be provided in Information on Precautions, etc. to minimize the risk of distal embolization that could cause delayed flow, guidewire malfunctions (e.g., guidewire fracture) that could lead to distal embolization, and vascular dissection (vessel injury). As part of post-marketing safety measures, training programs will be offered for the proper use of the product to minimize the risk. In addition, the events mentioned above will be monitored and evaluated through a use-results survey.

PMDA's view:
In the clinical study, the delayed flow events in the 2 patients resolved without additional procedures, and did not result in worsening of clinical symptoms; however, depending on the location and range of distal embolization with debris generated by ablation using the product, and the blood circulation in the affected limb, ischemia could worsen, which may lead to serious events such as exacerbation of symptoms or limb amputation. In the use of the product, which mechanically ablates calcified lesions, the risk of ablation debris-associated distal embolization is inevitable. In order to maintain the product's risk-benefit balance, the following factors are considered important for safety measures, in addition to the points explained by the applicant:

- Eligible patients must be carefully selected. Appropriately identify high-priority patients for atherectomy using the product, and avoid those with potential risks of embolization-associated serious clinical events, etc.

- The risk of distal embolization increases with the ablation length. Ablation should be limited to the area where it is clinically required.
- The clinical study revealed the occurrence of delayed flow for which a causal relationship to the product (e.g., guidewire fracture) could not be ruled out. Delayed flow may lead to serious adverse events. Appropriate product usage should be advised and thoroughly disseminated through training opportunities, etc.
- The use of the product involves potential risks of delayed flow and distal embolization. The specified proper product usage must be adhered to and actions to take against these events should be thoroughly learned through training programs.
- The product should be used only by physicians with experience in lower extremity artery atherectomy who have competent skills to respond to complications promptly, including endovascular treatment of below-the-knee and foot arteries.

In the clinical study, vascular dissection occurred in 3 patients, 2 of whom did not undergo re-intervention at 24 weeks after the trial procedure. The other patient underwent re-intervention at 165 days after the trial procedure. Vascular dissection in all 3 patients did not lead to serious outcomes. However, vascular dissection is a critical event that can affect the establishment of antegrade flow to the foot and the outcome of balloon angioplasty. Therefore, cautionary advice on the product use should be disseminated via Information on Precautions, etc. and thoroughly understood through training programs. In addition, the use of the product should be to limited physicians who are adequately skilled to response to complications immediately. The risks of concern can be minimized by implementing these measures.

6.B.(3).2).(b) Malfunctions

Among malfunctions reported, 2 critical events of "guidewire fracture, retained fragments" were reported in 2 patients. Delayed flow for which a causal relationship to the malfunction could not be ruled out occurred in one of the patients. PMDA asked the applicant to provide an explanation as to whether the risk associated with the malfunctions reported in the clinical study is acceptable.

The applicant's explanation:

Of the reported events "guidewire fracture, retained fragments," in one of the patients (patient No. 1), wire fracture and retained fragments were observed by fluoroscopy and angiography after the removal of the device from the plantar artery. In the other patient (patient No. 13), when the guidewire was replaced with a different one and the burr was inserted, the guidewire fractured, leaving a fragment in the distal part of peroneal artery. The physician primarily responsible for the procedure in which the malfunction occurred had experiences with the "Rotablator" in the coronary artery region of approximately 20 patients. According to the investigation conducted by

Headquarters in the US, the exact causes of the 2 guidewire fracture and retention events could not be determined; however, it was suggested that the guidewire may have become trapped in the lesion, etc., causing excessive overload leading to fracture, or that the burr rotation in a fixed position may have resulted in guidewire fracture. Furthermore, the additional data on the malfunction from the medical institution suggested the possibility that the guidewire was not locked or held securely, which made the guidewire unstable and damaged by burr interference, resulting in fracture. Therefore, before rotating the burr, the guidewire should be carefully observed fluoroscopically to ensure that the guidewire tip is not trapped in the area of the calcified lesion or in a narrow part of the vessel; the wire clip should be attached correctly to the guidewire; the device should be securely held; and the rotation of the burr in a fixed position should be avoided. The importance of these instructions will be communicated via Information on Precautions, etc. and in the training program that will be implemented as part of post-marketing safety measures to minimize the risk.

In a survey[21] on the incidence of malfunctions with the "Rotablator" and the determinants of complications in rotational atherectomy conducted using the nationwide registration system (J-PCI) in Japan, the incidence of malfunctions was 1.86% in low-volume institutions (1 to 10 rotational atherectomy cases over 2 years), 1.59% in middle-volume institutions (11 to 24 rotational atherectomy cases), and 1.06% in high-volume institutions (25 to 564 rotational atherectomy cases). The survey shows that the incidence of malfunctions in high-volume institutions was approximately half of that in low-volume institutions, suggesting that it is important not only for the physicians but also for the entire medical institution (team of healthcare professionals involved in the procedure with the "Rotablator") to participate in training programs and gain experience in treatment in order to minimize the risk of malfunctions and adverse events. Although this survey was on atherectomy for coronary artery intervention using the "Rotablator," it can be predicted that there will be a similar trend for peripheral intervention; therefore, participation in training programs and experiences in the treatment using the product will lead to the minimization of risks of malfunctions and adverse events in peripheral intervention.

PMDA's view on device malfunctions:
The events of "guidewire fracture, retained fragments" (11.8%) reported in the clinical study occur depending on the position where the guidewire is delivered and operative technique. The applicant views that thorough communication of the background of these events and training on proper use of the product will help reduce these risks, and this view is reasonable. In addition, given that these malfunctions were also reported from physicians with experience with the "Rotablator" for coronary arteries in the study, the following additional measures must be taken to minimize risks:

- Thoroughly communicate the possibility that the vascular course of below-the-knee arteries and lesion location may influence the occurrence of malfunctions.
- To minimize the risk of malfunctions, specify the characteristics of below-the-knee artery lesions recommendable for the treatment, such as proximal side lesions with no tortuosity as low risk lesions selected for less experienced physicians, and develop a training plan taking into account the learning curve.

It is important that physicians handling the product not only have a good understanding of product characteristics but also is familiar with the characteristics of below-the-knee artery lesions of CLTI and endovascular treatment. The incidences of guidewire fracture and retained fragments were higher than those in peripheral vessels reported overseas (guidewire fracture, 0.014%; guidewire detachment, 0.012%; unretrievable device fragments, 0.002%). This is probably due to the small sample size of the RESCUE-BTK study and the fact that many Japanese patients with CLTI are on dialysis and have severely calcified lesions. Based on the discussions at the Expert Discussion, it has been concluded that the incidence can be lowered by implementing the risk minimization measures above.

In addition to guidewire fracture and retained fragments, events related to difficulty in device removal (burr caught on guidewire, 0.041%; burr lodged in lesion, 0.014%), which were not observed in the study, were reported overseas. Analyses suggested that tortuous vessels and the use of larger burr size may be associated with increased risk of difficulty in device removal. It is considered appropriate to give caution via Information on Precautions, etc. based on the analysis results, and it is important to thoroughly communicate the risk through training programs.

Because of the limited number of patients evaluated in this study, safety data should be carefully evaluated in the use-results survey.

6.B.(3).2).(c) Other safety evaluation

The applicant's explanation about the incidence of re-intervention that was 35.3% (6 of 17 patients) at 24 weeks post-trial procedure in the RESCUE-BTK study (Table 17):

In the OLIVE registry study,[22] a prospective, multicenter study conducted in Japan in 314 patients with CLTI, 27% and 37% underwent re-intervention at 6 months and 12 months, respectively. In the J-BEAT Angio registry study,[23] a prospective, multicenter study conducted in CLTI, clinical data from 63 patients in Japan (68 limbs, 58 of them had tissue loss) following endovascular treatment of isolated below-the-knee lesions were evaluated. In this study, 40% of limbs and 48%

of limbs underwent re-intervention within 3 months and 12 months, respectively. Although it is difficult to simply compare the results of studies conducted in patients with different characteristics, the re-intervention rates in the RESCUE-BTK study are comparable to those of the OLIVE registry and J-BEAT Angio registry studies, both of which were conducted in patients with CLTI in whom balloon angioplasty was possible. Therefore, it is considered that the re-intervention rates in the RESCUE-BTK study are clinically acceptable.

PMDA's view on the re-intervention in the RESCUE-BTK study:
The study targeted patients with CLTI who had below-the-knee arterial lesions. In the study, re-intervention was performed ≥100 days after the trial procedure except for 1 patient (68 days), and the residual stenosis was <50% after re-intervention, indicating a certain level of patency. Data from Japanese literature[22] show that balloon angioplasty is performed approximately once every 3 months, and given this, the study results are comparable to the current treatment outcomes in Japan and acceptable.

The safety results of the study revealed deaths of 2 patients (11.8%) due to ischemic cardiomyopathy and pneumonia by 24 weeks post-trial procedure. However, these events are considered acceptable because their causal relationship to the procedure or device was ruled out, and the events were unlikely to be attributable to the product use. Adverse events associated with the procedure or device were all related to device malfunctions or re-intervention, except for calcium chondrocalcinosis pyrophosphate, for which a causal relationship to the procedure or device could not be ruled out because of its unknown cause.

6.B.(3).3) Intended patients

As described earlier in Section "6.B.(3).2).(a) Delayed flow, distal embolization, and vascular dissection," the Peripheral Rotablator PRO is intended for use in patients with CLTI suffering from critical limb ischemia. When procedure-induced distal embolization leads to a clinically serious event, balloon angioplasty will fail and even lead to increased risk of wound exacerbation or limb amputation due to unestablished blood flow to the foot. Therefore, careful selection of patients needing the treatment with the product is essential to maintain a favorable benefit-risk balance.

One of the inclusion criteria for the registered study participants was unsuccessful pre-trial balloon angioplasty (balloon crossing or dilatation failure). PMDA asked the applicant to explain the rationale for this criterion, in relation to the information about lesion characteristics and types of balloons used in pre-trial balloon angioplasty (Table 19).

Table 19. Data on lesions and balloons used in pre-trial balloon angioplasty

Patient No.	Reference vessel diameter (mm)	Lesion length (mm)	Balloon diameter (mm)	Balloon length (mm)	Eligibility assessment	Pre-trial balloon angioplasty[1]
1	2.5	70	1.5	40.0	Balloon uncrossable	-
			2.0	40.0	Balloon uncrossable	-
			2.0	40.0	Balloon uncrossable	-
			2.5	120.0	Balloon uncrossable	-
2	2.5	50	2.0	40.0	Balloon uncrossable	-
			2.5	40.0	Balloon uncrossable	-
			2.5	40.0	Balloon uncrossable	-
3	3.0	30	2.0	200.0	Balloon uncrossable	-
4	3.0	70	3.0	100.0	Balloon uncrossable	-
5	3.0	45	2.5	100.0	Balloon uncrossable	-
6	3.0	30	3.0	210.0	Balloon uncrossable	-
7	2.4	40	2.0	200.0	Balloon uncrossable	-
8	2.5	98	2.5	100.0	Balloon uncrossable	-
9	2.5	99	2.5	100.0	Balloon uncrossable	-
10	2.5	90	2.0	100.0	Balloon uncrossable	-
11	(proximal) 4.0	15	3.0	20.0	Undilatable	Regular type balloon 14 atm
	(distal) 2.5	90	2.0	100.0	Undilatable	Pressure-resistant balloon 30 atm
12	2.0	80	2.0	100.0	Undilatable	Pressure-resistant balloon 20 atm
13	3.5	80	2.5	20.0	Balloon uncrossable	-
14	(proximal) 2.0	20	2.0	100.0	Balloon uncrossable	-
	(distal) 2.0	20	2.0	100.0	Undilatable	Regular type balloon 22 atm
15	2.5	25	2.0	250.0	Undilatable	Regular type balloon 1 atm
16	2.5	20	2.0	210.0	Undilatable	Regular type balloon 6 atm
17	2.5	80	2.0 1.5	100.0 120.0	Balloon uncrossable Balloon uncrossable	- -

[1.] Additional data obtained from the medical institutions

The applicant's explanation:

In the pre-trial balloon angioplasty in the study, 13 patients (13 lesions) were assessed as "balloon uncrossable" by the core laboratory. The protocol of the study specifies that the balloon diameter should not exceed the target vessel diameter by visual inspection. In all 13 patients whose balloon angioplasty was assessed as "balloon uncrossable," the diameter of the balloon used was either the same or smaller than that of the reference vessel. Conversely, balloon length was not specified in the protocol, and balloons in length more than twice the lesion length were used in 5 of 13 patients who were assessed as "balloon uncrossable." Additional inquiries to the medical institutions confirmed that longer balloons had been selected for the 5 patients because of their

long target lesions requiring longer balloons to cover the entire length. Also, in this study, the reported lengths of lesions that underwent partial ablation with the product before balloon angioplasty were actually the lengths of ablated segments, not the lengths of whole lesions.

In the assessment by the core laboratory, 5 patients (6 lesions) were assessed as “undilatable ” The protocol of the RESCUE-BTK study did not specify the types of balloon that should be used for pre-trial balloon angioplasty. In general, while pressure-resistant balloons are characterized by their superior ability to dilate highly calcified lesions, their crossability is slightly low. In clinical practice, therefore, a suitable balloon is selected for each lesion taking into account the length, degree of calcification, crossability, safety (risk of vascular dissection), etc. Additional inquiries to the medical institutions about the cases with undilatable lesions revealed the types of balloons used for the pre-trial balloon angioplasty as follows; incomplete dilatation despite the use of pressure resistant balloons in 2 lesions of 2 patients, 2 lesions of 2 other patients expanded up to 14 atm and 22 atm, respectively, but remained incomplete without using pressure-resistant balloons out of consideration for crossability, 2 lesions of the remaining 2 patients, severely calcified, treated without using pressure-resistant balloons to prioritize crossability, which were expanded at lower-than-recommended pressures. For each lesion, the optimal balloon type and size were selected, and balloon angioplasty was performed at optimal expansion pressures. These measures, however, resulted in incomplete expansion.

PMDA’s view on the determination of success or failure of pre-trial balloon angioplasty in this study:

In each of the 3 patients in whom balloon crossing failed (3 lesions; patient No. 1, 2, and 17), in the pre-trial balloon angioplasty, the diameter of the first balloon was less than the reference vessel diameter. For the subsequent balloons, crossing was attempted by changing the balloon diameter and length. This indicates that balloon size was selected more strictly for patients with balloon uncrossable lesions. Other cases include the use of balloons longer than the length of the lesion to be ablated, and the possibility cannot be ruled out that balloons could have passed through the lesion if a more suitable balloon size was selected. Patients with difficult dilatation included 3 patients (4 lesions; patient Nos. 11, 12, and 14) who had undergone expansion with either regular-type balloons at high pressure or pressure-resistant balloons, which is considered appropriate. However, 2 patients (2 lesions; patient Nos. 15 and 16) were treated with regular-type balloons at lower pressures, and the possibility cannot be ruled out that expansion might have succeeded under higher pressure. Considering that 6 of 17 cases (patient No. 1, 2, 11, 12, 14, and 17) in the study can be objectively determined as “balloon uncrossable” or “balloon undilatable,” these patients had more severely calcified lesions among those enrolled in this study. The efficacy and

safety of the product in these patients were evaluated.

In terms of the primary endpoint, balloon angioplasty was assessed as successful in all patients. However, in 1 patient (patient No. 17), delayed flow, which was suggested to have been caused by distal embolization, was noted. In all 17 patients, VAS, SPP, Rutherford classification, and EQ-5D-5L improved at 24 weeks post-trial procedure, and improvement in these parameters was also noted in the majority of the 6 patients. Wound healing was noted in 4 of 6 patients at 24 weeks post-trial procedure.

Safety data show that vascular dissection occurred in 1 of 6 patients, and at 24 weeks post-trial procedure, re-occlusion and re-intervention occurred in 2 patients each. Adverse events associated with the procedure or device occurred in 1 of 6 patients. Compared to the overall results for the 17 patients, no significant safety concerns were noted in these 6 patients, and it was concluded that safety is acceptable.

Taken together, the study results demonstrated the efficacy and safety of the product. Although in the extremely limited number of patients, the results suggest comparable efficacy and safety for highly severely calcified lesions that impede balloon crossing or inflation. The product is clinically positioned as a medical device that enables balloon angioplasty in patients with CLTI whose below-the-knee lesions are unlikely to respond to the current procedure and have no other effective treatment options. Thus, it is important to take the measures as mentioned later in Section "6.B.(5) Post-marketing safety measures" and carefully select patients to be treated with the product. This advice should be offered in Information on Precautions, etc., taking into account the comments from the Expert Discussion.

6.B.(4) Intended use

Based on the study results, the use of the Peripheral Rotablator PRO will enable successful balloon angioplasty in patients with CLTI in whom balloon angioplasty for below-the-knee arterial lesions fails. However, risks such as distal embolization due to ablation debris from calcified lesions are theoretically inevitable. The use of the product should be, therefore, limited in patients with CLTI with high priority for endovascular treatment in whom these risks are deemed acceptable. In addition, given the clinical positioning of the product, it is appropriate to specify target lesions as below-the-knee calcified lesions impeding the crossing or inflation of PTA balloon.

Based on the above, PMDA concluded that the "intended use or indication" of the product should be as shown below:

Intended use or indication (Underline denotes changes)

The Peripheral Rotablator PRO is intended for adjunctive use in endovascular treatment for patients with chronic limb-threatening ischemia. The product percutaneously approaches calcified lesions in the below-the-knee arteries that impede the crossing or inflation of balloon catheter for percutaneous transluminal angioplasty, thereby ablating atherosclerotic plaques or stenotic lesions.

6.B.(5) Post-marketing safety measures

The Peripheral Rotablator PRO, an atherectomy device intended for use in below-the-knee calcified lesions in patients with CLTI, is the first product to be introduced into Japan. In the "Jetstream Atherectomy System" (Approval No. 30300BZX00287000), an approved atherectomy device intended for use in the superficial femoral artery (proximal to the present device) and/or the proximal popliteal artery, after the use-results survey was completed, the following cases were reported for the above device. In one case of general use, due to distal embolization, for which bailout was not possible, intermittent claudication occurred and the patient finally had to undergo a major amputation. In another patient with CLTI, lower limb gangrene occurred and resulted in death. In response, the Guidance for Use[24] was published by the relevant academic societies, and the proper use guidelines were revised.[25] In light of greater caution currently required for the determination of patient eligibility, PMDA considers that the following points are essential to ensure the effective and safe introduction of the Peripheral Rotablator PRO into Japan:

1) The product should only be used in carefully selected eligible patients at high risk for surgical bypass procedures who are expected to benefit from balloon angioplasty. The procedure must only be performed by physicians and medical teams with expertise in the treatment of CLTI as well as sufficient knowledge and experience in endovascular treatment of below-the-knee arteries and postoperative management.
2) Physicians must have necessary skills and knowledge to operate the product effectively and safely.
3) Physicians must have necessary skills and knowledge to deal with product-associated complications and adverse events (in particular, delayed flow, distal embolization, and vascular dissection) as well as post-operative management following balloon angioplasty (including appropriate foot care such as wound management) for prompt action including surgical procedures.
4) Based on the post-marketing treatment outcomes with the product, the applicant should periodically review the proper use guidelines and take additional safety measures promptly.

PMDA's view:

In the context of 2) and 3) above, the applicant's product training (Table 20) will provide knowledge specific to the peripheral vascular field and strategies for complication management to the participants including team members involved in the procedure using the product, which is considered appropriate. The proper use guidelines (Table 21) drafted by the relevant academic societies (Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Vascular Surgery, and Japanese Society of Interventional Radiology) are expected to facilitate the use of the product by physicians with sufficient experience in the treatment targeting CLTI and lower limb atherectomy, and at medical institutions capable of handling complications and post-operative management. Thus 1) through 4) above are appropriate. Taking into account the comments from the Expert Discussion, it was decided that these requirements be attached as Approval Condition 1.

Table 20. Outline of training

Category	Detail (intended persons)
Lecture	• Product overview: morphology, structure, and principle of the product • Directions for use: from preparation to end of procedure, characteristics of procedure with the product in peripheral regions, precautions for use, troubleshooting, bailout technique for complications, procedure case videos (after completion of use-results survey) • Summary of clinical study: summary of the RESCUE-BTK study (including complications and how to respond to them) • Proper use guidelines: explanation of the guidelines (Physicians who perform the procedure using the product, supporting physicians, and professional catheterization team)
Hands-on training	• Understanding and learning the operative procedure using the actual product (Physicians who perform the procedure using the product and supporting physicians)

Table 21. Summary of proper use guidelines (draft)

Category	Detail
Indication	All the following requirements must be met: • Patients: patients at increased risk for surgical bypass procedures (patients who are not expected to live <2 years, without favorable autogenous veins), who are expected to benefit from PTA balloon treatment • Affected limb: Rutherford category 4 or 5 for ischemic limb • Anatomical position: lesion located in the proximal two-thirds of the below-the-knee arteries • Lesion: severe calcified lesion (bilateral calcification), even a balloon of suitable size cannot cross the lesion, or lesion with expected residual stenosis of ≥75% after balloon angioplasty • Arteries distal to the ankle joint: good runoff must be present in the arteries distal to the ankle joint for the planned ablation of the arterial lesion * Whenever possible, by CT, etc., confirm that the stenotic/occlusive lesion is either a calcified nodule or superficial nodule lesion, and no thrombus is present (the device is not indicated for thrombus) **Points to note** In the clinical study conducted in Japan, efficacy and safety of the product have not been evaluated for the following lesions: - Rutherford category 6 in affected limb - In-stent restenosis - Lesion length ≥10 cm * In the investigator-initiated study, Rutherford category 6 was excluded. Although the target lesion length was <10 cm in the study, in clinical use, procedure with the device should be limited to local use, from the standpoint of preventing distal embolization. The risk of slow flow increases when with longer ablation lengths. * Because of its structure, there is an inherent risk of distal embolization (blood flow obstruction persists despite pharmacologic treatment, and requires additional endovascular procedure, such as thrombus aspiration and balloon inflation") associated with an atherectomy device and is unavoidable. In particular, it is difficult to take preventive measures for distal embolization for lesions in below-the-knee arteries, which have a small diameter. Furthermore, because the target disease is CLTI, many patients have poor peripheral vascular beds, making recovery from distal embolization-related blood flow disturbances difficult. Based on the above factors, it is desirable to keep the ablation distance as short as possible. * If distal embolization occurs, this should be reported in detail in a form and submitted to the Committee. * In addition to the distal embolization risk described above, the operator must keep in mind that the device can be used only after risks and benefits associated with the use of the atherectomy device are fully explained to the patient.
Requirements for physician	Physicians who meet all of the following requirements: • The eligible physician must be one of the following: Fellow of the Japanese Association of Cardiovascular Intervention and Therapeutics, Board Certified Specialist of Japanese Society of Interventional Radiology, or Certified Endovascular Specialist of the Japanese Society for Vascular Surgery • The physician must complete the training program for the product • The physician must have experience in below-the-knee endovascular procedures in at least 50 patients

Requirements for medical institution	Medical institutions that meet all of the following requirements: • The eligible medical institution must be one of the following: Certified Training Facility or Related Facility of the Fellow of the Japanese Association of Cardiovascular Intervention and Therapeutics, Training Facility of Japanese Society of Interventional Radiology, Certified Training Facility of the Japanese Board of Cardiovascular Surgery • The operating room or angiography room must be permanently equipped with DSA • The medical institution must be able to provide emergency surgery in the event of treatment difficulties, complications, malfunctions, etc. or be able to collaborate with other institutions that can provide such measures • The medical institution must have an emergency system that is integrated with the surgical department to allow atherectomy- or balloon angioplasty-induced complications to be responded to promptly • There must be a foot care team that can provide medical care for CLTI
Proper use	Standard procedures are specified

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Table 22 shows the outline of the use-results survey, which is planned to be conducted to evaluate the safety and efficacy of the Peripheral Rotablator PRO in clinical use after the product launch.

Table 22. Use-results survey plan

Objective	This survey is conducted as a general use-results survey, to monitor the incidence of malfunctions by type, and detect/confirm the quality, safety, and efficacy-related data in clinical use after the product launch.
Study population	Patients for whom the product is used in accordance with the intended use, indication, and directions for use specified in the approval. Data will be collected from all patients in whom the product is tried, and no inclusion/exclusion criteria will be established (whether the target lesion is appropriate or not will be assessed by a third party consisting of physicians selected by the Atherectomy Device Committee consisting of relevant academic societies).
Survey period	Survey period: 48 months (4 years) after the acquisition of marketing authorization Preparation for marketing: 14 months; patient registration period: 12 months; follow-up period: 12 months; data collection/analysis: 10 months
Planned sample size	50 patients **Rationale:** In the RESCUE-BTK study, the incidence of distal embolization was 5.9% at final confirmatory angiography by core laboratory assessment. Assuming an approximate, expected incidence of 5.9%, a sample size of 50 will allow the detection of at least 1 case at a probability of 95%.
Survey method	All-case survey
Key survey items	Vascular dissection, vessel perforation, distal embolization Guidewire fracture, retained guidewire fragments, difficulty in guidewire/burr removal
Survey items	1. Baseline: 1) Patient characteristics (frailty scale, albumin level, C-reactive protein, medical history, wound assessment, WIfI classification, Rutherford classification, ABI, SPP, co-administered drugs) 2. Lesion/procedure data 1) Characteristics of lesion (target limb, target vessel, target lesion site, reference vessel diameter, percent diameter stenosis, target lesion length [ablation length], calcification, run-off [below-the-knee artery, foot]) 2) Procedure data (device data [e.g., Peripheral Rotablator PRO, final device], run-off [target vessel, foot]), vascular dissection, vessel perforation, distal embolization, delayed flow, residual stenosis, procedural success/failure, co-administered drugs 3. Follow-up: postoperative, 1 month, 3 months, 6 months, and 12 months after procedure 1) Postoperative (hospital admission/discharge, Duplex ultrasonography exam, ABI, SPP, co-administered drugs) 2) Follow-up (Duplex ultrasonography exam, wound assessment, WIfI classification, Rutherford classification, ABI, SPP, co-administered drugs)

	4. Adverse events (e.g., vascular dissection, vessel perforation, distal embolization, re-intervention, target limb major/minor amputation, cardiovascular events) 5. Malfunctions (e.g., guidewire fracture, retained guidewire fragments, difficulty in guidewire/burr removal)

7.B Outline of the review conducted by PMDA

The Peripheral Rotablator PRO, an atherectomy device intended for use in below-the-knee calcified lesions in patients with CLTI, is the first product to be introduced into Japan. The efficacy and safety of the product were evaluated in the RESCUE-BTK study, but in limited number of patients. Therefore, it is important to continue assessment through the use-results survey to ensure the practices of appropriate product use and patient selection in the post-marketing, as well as safe and effective use of the product for below-the-knee calcified lesions in patients with CLTI in whom balloon angioplasty alone has been unsuccessful. Careful implementation is important with safety ensured. Critical adverse events, particularly distal embolization, should be reported to the relevant academic societies, evaluated and informed. Necessary additional risk mitigation or proper-use measures should be taken promptly.

The applicant's decision on third-party verification to ensure eligibility of patients selected for the survey, i.e., patients with CLTI for whom balloon angioplasty is unlikely to succeed, is acceptable.

It is appropriate to set the sample size based on the incidence of distal embolization, a clinically important adverse event. Given the examples of the "Jetstream Atherectomy System" mentioned in Section "6.B.(5) Post-marketing safety measures," it is expected that eligibility of lesions and patients will be carefully determined after the product launch, and the proposed sample size is thus acceptable.

In view of the situation of the similar device mentioned, the implementation of additional safety measures should be considered promptly in case of distal embolization, etc. reported in the post-marketing use results. Accordingly, the use of the Peripheral Rotablator PRO should be restricted to the medical institutions involving in the use-results survey at the introductory phase of the product. The restriction should be eased in the future based on the incidence of distal embolization and other events in the survey population to expand the product use to other medical institutions.

Although the number of eligible patients will be limited, the proposed survey period is acceptable.

The guidelines[3] recommend the use of comprehensive limb severity classification systems, such as the Wound, Ischemia, and foot Infection (WIfI) classification, (Recommendation Class I, evidence level C) to classify the CLTI disease stage. It is thus appropriate to include the WIfI

classification as a survey item in addition to the endpoints evaluated in the clinical study.

In view of the other survey items specified, the applicant's use-results survey plan (draft) is appropriate, and the survey will be attached as Approval Condition 2.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Information on Precautions, etc., provided that the applicant advises necessary caution.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

PMDA's conclusion concerning the results of the on-site GCP inspection

The medical device application data (*he*-1-1 Clinical Study Report) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, it was confirmed that the study was generally conducted in compliance with the GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application

documents submitted. The inspection revealed the following findings requiring corrective action at some of the study sites. Although the issues had no significant impact on the overall assessment of the clinical study, the heads of the relevant medical institutions and the applicant were notified of the issues as the findings requiring corrective action.

Findings requiring corrective action

Study sites

- The heads of the medical institutions received a notification on the study device from the investigator that was relevant to Article 80-2, paragraph 6 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. However, they failed to seek opinions of the Institutional Review Board about whether to continue the trial at their medical institutions.
- Following the reception of audit reports, the heads of the medical institutions failed to seek opinions of the Institutional Review Board about the appropriateness of some parts of the trial conducted at their medical institutions.

IV. Overall Evaluation

The application review for the Peripheral Rotablator PRO primarily focused on (1) efficacy and safety and (2) post-marketing safety measures. Taking into account the comments from the Expert Discussion, PMDA have reached the following conclusions.

(1) Efficacy and Safety

In the investigator-initiated study conducted to evaluate the safety and efficacy of the preceding "Rotablator," as an adjunctive device for patients with CLTI with previous unsuccessful balloon angioplasty, the primary endpoint of "procedural success rate of balloon angioplasty after the trial procedure" was 94.1% (16 of 17 patients) (95% CI, 71.3%-99.9%), which met the prespecified target of 50%. No patients underwent major amputation of the affected limb within 24 weeks of the procedure. The improvements in VAS, SPP, Rutherford classification, and EQ-5D-5L were maintained. The proportion of patients achieving wound healing was 50% (6 of 12 patients) and the proportion of healed wounds 66.7% (12 of 18 patients), demonstrating the efficacy of balloon angioplasty in below-the-knee arteries in patients with CLTI. At the same time, product-specific events including delayed flow, distal embolization, and vascular dissection, and device malfunctions including guidewire fracture or retained fragments were observed at a certain frequency. It is inherently difficult to completely avoid distal embolization owing to the ablation using the product. Embolization can lead to severe events including limb amputation, depending on its extent and the patient's condition, and careful selection of high-priority patients is, therefore, essential for the treatment with the product. Risks of other adverse events and malfunctions can be minimized through thorough communication about proper device use and learning-curve based training programs, etc. The study results suggested the product's efficacy and safety also in cases of highly severely calcified balloon-uncrossable or -undilatable lesions. It is thus clinically meaningful that the product enables successful revascularization for CLTI patients with high priority for endovascular treatment for below-the-knee arteries, and it is useful to make the product available in Japan.

(2) Post-Marketing Safety Measures

The Peripheral Rotablator PRO is the first atherectomy device to be introduced into Japan to treat below-the-knee calcified lesions in patients with CLTI. For its effective and safe launch, it is important that eligible patients, i.e., those at high risk for surgical bypass procedure for whom balloon angioplasty would be beneficial but unlikely to succeed, are carefully selected by physicians and medical teams with sufficient knowledge and experience in endovascular treatment of below-the-knee arteries and lower limb atherectomy, as well as expertise in CLTI treatment. Risks such as distal embolization and vessel injury are inevitable with the use of the product, and guidewire fracture or other malfunctions can occur depending on how it is used.

Therefore, the procedure involving the product should be performed at medical institutions with established emergency system to respond to these events, and by physicians who have gained necessary skills and knowledge about the product and the procedure. To this end, it is important to adhere to the proper use guidelines prepared by the relevant academic societies. These requirements should be attached as Approval Condition 1.

Also important are continual evaluation of product safety and efficacy through the use-results survey based on data on distal embolization and other adverse events as well as malfunctions associated with the product, and additional post-marketing safety measures promptly taken when necessary. Therefore, the applicant should conduct the survey covering all patients treated with the product until data are accrued from a specified number of patients. This should be attached as Approval Condition 2. The period for the use-results survey should be 4 years (pre-launch preparation, 14 months; patient registration: 12 months; observation: 12 months; data collection/analysis: 10 months).

On the basis of the above reviews, PMDA has concluded that the product may be approved for the following intended use.

Intended Use

The Peripheral Rotablator PRO is intended for adjunctive use in endovascular treatment for patients with chronic limb-threatening ischemia. The product percutaneously approaches calcified lesions in the below-the-knee arteries that impede the crossing or inflation of balloon catheter for percutaneous transluminal angioplasty, thereby ablating atherosclerotic plaques or stenotic lesions.

Approval Conditions

1. The product should only be used for eligible patients selected by physicians and medical teams with adequate knowledge and experience in endovascular treatment for chronic limb-threatening ischemia as well as necessary operational skills with the product and knowledge about procedure-related complications, at medical institutions with an established treatment system. To this end, the applicant is required to take appropriate measures including the provision of training programs and the dissemination of the proper use guidelines jointly prepared with relevant academic societies.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are accrued from a specified number of patients, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 4 years.

PMDA has concluded that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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